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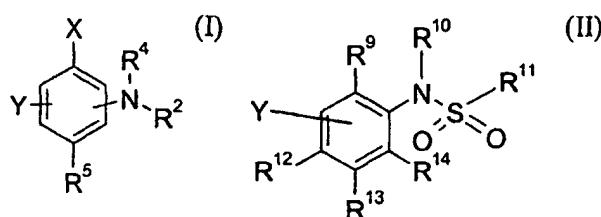
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**WO 02/092585 A1**

(54) Title: NOVEL, ARYLSUSFONAMIDE COMPOUNDS FOR THE TREATMENT OF OBESITY, TYPE II DIABETES AND CNS-DISORDERS



(57) Abstract: The present invention relates to substituted bis-arylsulfonamide and arylsulfonamide compounds of the general formula (I) or the formula (II), which compounds are potentially useful for the prophylaxis and treatment of medical conditions relating to obesity, type II diabetes and/or disorders of the central nervous system.

**NOVEL, ARYLSULFONAMIDE COMPOUNDS FOR THE TREATMENT OF OBESITY, TYPE II  
DIABETES AND CNS-DISORDERS**

**RELATED APPLICATIONS**

This application claims priority to Swedish application number 0101660-9, filed on  
5 May 11, 2001, U.S. provisional application number 60/294,102, filed on May 29, 2001, and  
U.S. provisional application number 60/294,132, filed on May 29, 2001, the contents of  
which are incorporated herein by reference.

**TECHNICAL FIELD**

10

The present invention relates to substituted bis-arylsulfonamide and arylsulfonamide compounds, to pharmaceutical compositions comprising these compounds, and to the use of the compounds for the prophylaxis and treatment of medical conditions relating to obesity, type II diabetes and/or disorders of the central nervous system.

15

**BACKGROUND ART**

Obesity is a condition characterized by an increase in body fat content resulting in excess body weight above accepted norms. Obesity is the most important nutritional disorder  
20 in the western world and represents a major health problem in all industrialized countries. This disorder leads to increased mortality due to increased incidences of diseases such as cardiovascular disease, digestive disease, respiratory disease, cancer and type II diabetes. Searching for compounds, which reduce body weight has been going on for many decades.  
25 One line of research has been activation of serotonergic systems, either by direct activation of serotonin receptor subtypes or by inhibiting serotonin reuptake. The exact receptor subtype profile required is however not known.

Serotonin (5-hydroxytryptamine or 5-HT), a key transmitter of the peripheral and central nervous system, modulates a wide range of physiological and pathological functions, including anxiety, sleep regulation, aggression, feeding and depression. Multiple serotonin  
30 receptor subtypes have been identified and cloned. One of these, the 5-HT<sub>6</sub> receptor, was

cloned by several groups in 1993 (Ruat, M. et al. (1993) Biochem. Biophys. Res. Commun. 193: 268-276; Sebben, M. et al. (1994) NeuroReport 5: 2553-2557). This receptor is positively coupled to adenylyl cyclase and displays affinity for antidepressants such as clozapine. Recently, the effect of 5-HT<sub>6</sub> antagonist and 5-HT<sub>6</sub> antisense oligonucleotides to reduce food intake in rats has been reported (Bentley, J.C. et al. (1999) Br J Pharmac. Suppl. 126, P66; Bentley, J.C. et al. (1997) J. Psychopharmacol. Suppl. A64, 255).

Compounds with enhanced affinity and selectivity for the 5-HT<sub>6</sub> receptor have been identified, e.g. in WO 00/34242 and by Isaac, M. et al. (2000) *6-Bicyclopiperazinyl-1-arylsulfonylindoles and 6-Bicyclopiperidinyl-1-arylsulfonylindoles derivatives as novel, potent and selective 5-HT<sub>6</sub> receptor antagonists*. Bioorganic & Medicinal Chemistry Letters 10: 1719-1721.

#### DISCLOSURE OF THE INVENTION

It has surprisingly been found that the compounds of formula (I) and (II) show affinity for the 5-HT<sub>6</sub> receptor as antagonists at a low nanomolar range. Compounds according to the invention and their pharmaceutically acceptable salts have 5-HT<sub>6</sub> receptor antagonist activity and are believed to be of potential use in the treatment or prophylaxis of obesity and type II diabetes, as well as in the treatment or prophylaxis of disorders of the central nervous system such as anxiety, depression, panic attacks, memory disorders, sleep disorders, binge disorders, migraine, anorexia, bulimia, obsessive compulsive disorders, psychoses, Alzheimer's disease, Parkinson's disease, Huntington's chorea and/or schizophrenia, drug abuse, Attention Deficit Hyperactive Disorders (ADHD).

Definitions

Unless otherwise stated or indicated, the following definitions shall apply throughout the specification and the appended claims:

The term “C<sub>1-6</sub> alkyl” denotes a straight or branched alkyl group having from 1 to 6 carbon atoms. Examples of said lower alkyl include methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, t-butyl and straight- and branched-chain pentyl and hexyl.

5        The term “C<sub>1-6</sub> alkoxy” denotes a straight or branched alkoxy group having from 1 to 6 carbon atoms. Examples of said lower alkoxy include methoxy, ethoxy, n-propoxy, iso-propoxy, n-butoxy, iso-butoxy, sec-butoxy, t-butoxy and straight- and branched-chain pentoxy and hexoxy.

10        The term “halogen” shall mean fluorine, chlorine, bromine or iodine.

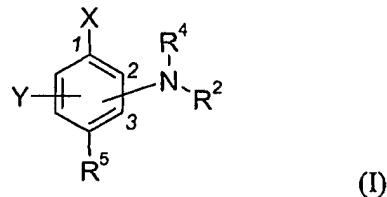
The terms “C<sub>4-6</sub> cycloalkyl” and “C<sub>3-7</sub> cycloalkyl” denote a cyclic alkyl group having a ring size from C<sub>4</sub> to C<sub>6</sub> or from C<sub>3</sub> to C<sub>7</sub>, respectively. Examples of said cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, methylcyclohexyl and cycloheptyl.

15

*Compounds of Formula I*

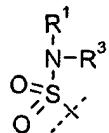
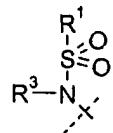
In a first aspect, this invention provides a compound of the general formula (I)

20



or a pharmaceutically acceptable salt thereof, wherein

X is



25

R<sup>1</sup> and R<sup>3</sup> are independently

- (a) H
- (b) C<sub>1-6</sub> alkyl,
- (c) C<sub>1-6</sub> alkoxy,
- 5 (d) straight or branched C<sub>1-6</sub> hydroxyalkyl,
- (e) straight or branched C<sub>1-6</sub> alkylhalides; or
- (f) a group Ar;

Ar is

- 10 (a) phenyl,
- (b) 1-naphthyl,
- (c) 2-naphthyl,
- (d) benzyl,
- (e) cinnamoyl,
- 15 (f) a 5 to 7-membered, partially or completely saturated, heterocyclic ring containing 1 to 4 heteroatoms, selected from oxygen, nitrogen and sulfur, or
- (g) a bicyclic ring system consisting of two heterocyclic rings as defined under (f), or a bicyclic ring system consisting of one benzene ring and one heterocyclic ring as defined under (f);

20 alternatively, R<sup>1</sup> and R<sup>3</sup> are linked to form a group (CH<sub>2</sub>)<sub>2</sub>O, (CH<sub>2</sub>)<sub>4</sub>O, or (CH<sub>2</sub>)<sub>3-5</sub> in formula (Ib);

optionally, the group Ar is substituted with

- 25 (a) Y, or
- (b) a 5 to 7-membered, partially or completely saturated, heterocyclic ring each containing 1 to 4 heteroatoms selected from oxygen, nitrogen or sulfur;

Y is

- 30 (a) H,
- (b) halogen,

- (c) C<sub>1-6</sub> alkyl,
- (d) CF<sub>3</sub>,
- (e) hydroxy,
- (f) C<sub>1-6</sub> alkoxy,
- 5 (g) C<sub>1-4</sub> alkenyl;
- (h) phenyl;
- (i) phenoxy,
- (j) benzyloxy,
- (k) benzoyl,
- 10 (l) OCF<sub>3</sub>,
- (m) CN,
- (n) straight or branched C<sub>1-6</sub> hydroxyalkyl,
- (o) straight or branched C<sub>1-6</sub> alkylhalides,
- (p) NH<sub>2</sub>,
- 15 (q) NHR<sup>6</sup>,
- (r) NR<sup>6</sup>R<sup>7</sup>,
- (s) NO<sub>2</sub>,
- (t) -CONR<sup>6</sup>R<sup>7</sup>,
- (u) NSO<sub>2</sub>R<sup>6</sup>,
- 20 (v) NR<sup>6</sup>COR<sup>7</sup>,
- (x) SO<sub>2</sub>NR<sup>6</sup>R<sup>7</sup>,
- (z) -C(=O)R<sup>6</sup>,
- (aa) -CO<sub>2</sub>R<sup>6</sup>, or
- (ab) S(O)<sub>n</sub>R<sup>6</sup>; wherein n is 0, 1, 2 or 3;

25

R<sup>2</sup> and R<sup>4</sup> are independently:

- (a) -SO<sub>2</sub>R<sup>1</sup>,
- (b) H,
- (c) C<sub>1-6</sub> alkyl,
- 30 (d) C<sub>1-C<sub>3</sub></sub> alkenyl,
- (e) C<sub>1-C<sub>3</sub></sub> alkylaryl,

(f) Ar as defined above for R<sup>1</sup>,

(g) -C(=O)R<sup>6</sup>,

(h) -C(O)NR<sup>6</sup>R<sup>7</sup>,

(i) -C(S)NR<sup>6</sup>R<sup>7</sup>,

5 (j) -CO<sub>2</sub>R<sup>6</sup>;

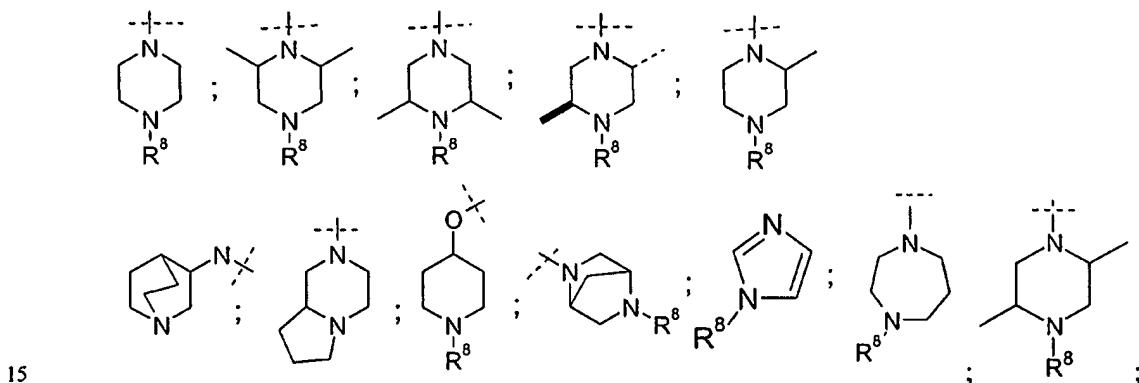
(k) -C(S)R<sup>6</sup>;

(l) straight or branched C<sub>1-6</sub> hydroxyalkyl, or

(m) straight or branched C<sub>1-6</sub> alkylhalides;

10 alternatively, R<sup>2</sup> and R<sup>4</sup> are linked to form a group (CH<sub>2</sub>)<sub>2</sub>O, (CH<sub>2</sub>)<sub>4</sub>O, or (CH<sub>2</sub>)<sub>3-5</sub> in formula (Ia);

$R^5$  is selected from the group consisting of the following chemical groups:



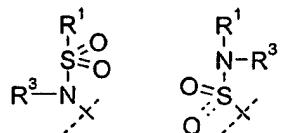
$R^6$  and  $R^7$  are independently  
(a) H,  
(b)  $C_{1-6}$  alkyl,  
20 (c)  $C_{3-7}$  cycloalkyl, or  
(d) Ar, as defined above in  $R^1$ ;

$R^8$  is

- (a) H, or
- (b)  $C_{1-6}$  alkyl.

5 Preferred compounds of the general formula (I) are those wherein:

X is



(la)

(lb)

10

$R^1$  is

- (e) a group Ar; or
- (f)  $C_{1-6}$  alkyl

15

Ar is

- (a) phenyl,
- (b) 1-naphthyl,
- (c) 2-naphthyl, or

20 (f) a 5 to 7-membered, partially or completely saturated, heterocyclic ring containing 1 to 4 heteroatoms, selected from oxygen, nitrogen and sulfur;

the group Ar is substituted with Y, wherein Y is

- (a) H,
- (b) halogen,
- (c)  $C_{1-6}$  alkyl,
- (d)  $CF_3$ ,
- (f)  $C_{1-6}$  alkoxy,

- (g) C<sub>1-4</sub> alkenyl;
- (h) phenyl;
- (l) OCF<sub>3</sub>, or
- (n) straight or branched C<sub>1-6</sub> hydroxyalkyl;

5

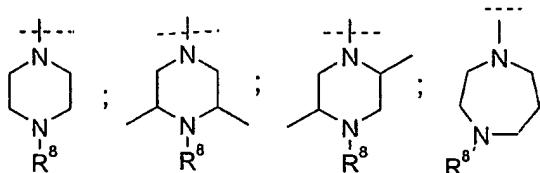
the group  $\begin{array}{c} \text{R}^4 \\ | \\ -\text{N}-\text{R}^2 \end{array}$  is attached to the phenyl ring in 2-position or in 3-position;

R<sup>2</sup> and R<sup>4</sup> are independently

- (a) H
- 10 (b) C<sub>1-3</sub> alkyl, in particular methyl or ethyl
- (c) -SO<sub>2</sub>R<sup>1</sup>; or
- (d) are linked to form a group (CH<sub>2</sub>)<sub>4</sub>O

R<sup>5</sup> is selected from the group consisting of the following chemical groups:

15



wherein R<sup>8</sup> is

- (a) H, or
- 20 (b) C<sub>1-6</sub> alkyl, in particular methyl.

R<sup>6</sup> and R<sup>7</sup> are independently

- (a) H,
- (b) C<sub>1-6</sub> alkyl,
- 25 (c) C<sub>3-7</sub> cycloalkyl, or
- (d) Ar.

N-[2-[ethyl(phenylsulfonyl)amino]-4-(4-methyl-1-piperazinyl)phenyl]benzenesulfonamide hydrochloride

3-fluoro-N-[2-{{(3-fluorophenyl)sulfonyl}amino}-4-(4-methyl-1-piperazinyl)phenyl]benzenesulfonamide hydrochloride

5 N-{4-(4-methyl-1-piperazinyl)-2-[(8-quinolinylsulfonyl)amino]phenyl}-8-quinolinesulfonamide hydrochloride hydrochloride

4-methyl-N-{4-(4-methyl-1-piperazinyl)-2-[(methylsulfonyl)amino]phenyl}benzenesulfonamide hydrochloride

10 N-{4-(1-piperazinyl)-2-[(phenylsulfonyl)amino]phenyl}-1-naphthalenesulfonamide hydrochloride

N-[2-[(phenylsulfonyl)amino]-4-(1-piperazinyl)phenyl]-8-quinolinesulfonamide hydrochloride

2-methyl-N-[2-[(phenylsulfonyl)amino]-4-(1-piperazinyl)phenyl]benzenesulfonamide hydrochloride

15 4-butoxy-N-[2-[(phenylsulfonyl)amino]-4-(1-piperazinyl)phenyl]benzenesulfonamide hydrochloride

5-fluoro-2-methyl-N-[2-[(phenylsulfonyl)amino]-4-(1-piperazinyl)phenyl]benzenesulfonamide hydrochloride

2-methoxy-4-methyl-N-[2-[(phenylsulfonyl)amino]-4-(1-

20 piperazinyl)phenyl]benzenesulfonamide hydrochloride

N-{4-(1,4-diazepan-1-yl)-2-[(phenylsulfonyl)amino]phenyl}benzenesulfonamide hydrochloride

N-{5-(1,4-diazepan-1-yl)-2-[(phenylsulfonyl)amino]phenyl}-N-ethylbenzenesulfonamide hydrochloride

25 N-{4-(1,4-diazepan-1-yl)-2-[(phenylsulfonyl)amino]phenyl}-2-naphthalenesulfonamide hydrochloride

N-{4-(1,4-diazepan-1-yl)-2-[methyl(phenylsulfonyl)amino]phenyl}benzenesulfonamide hydrochloride

N-{4-(1,4-diazepan-1-yl)-2-[(methylsulfonyl)amino]phenyl}-1-naphthalenesulfonamide

30 hydrochloride

N-{4-(1,4-diazepan-1-yl)-2-[(methylsulfonyl)amino]phenyl}-2-naphthalenesulfonamide hydrochloride

N-{4-(1,4-diazepan-1-yl)-2-[methyl(methylsulfonyl)amino]phenyl}-1-naphthalenesulfonamide hydrochloride

N-{4-(1,4-diazepan-1-yl)-2-[(phenylsulfonyl)amino]phenyl}-8-quinolinesulfonamide hydrochloride

5 N-{4-(1,4-diazepan-1-yl)-2-[(phenylsulfonyl)amino]phenyl}-2,4,6-trimethylbenzenesulfonamide hydrochloride

N-{4-(1,4-diazepan-1-yl)-2-[(phenylsulfonyl)amino]phenyl}-4-methylbenzenesulfonamide hydrochloride

N-{4-(1,4-diazepan-1-yl)-2-[(phenylsulfonyl)amino]phenyl}-2-methylbenzenesulfonamide hydrochloride

10 N-{4-(1,4-diazepan-1-yl)-2-[(phenylsulfonyl)amino]phenyl}-5-fluoro-2-methylbenzenesulfonamide hydrochloride

N-{5-(1,4-diazepan-1-yl)-2-[methyl(phenylsulfonyl)amino]phenyl}-4-methylbenzenesulfonamide hydrochloride

15 3-amino-4-(1,4-diazepan-1-yl)-N-(2-methoxyphenyl)benzenesulfonamide hydrochloride

3-amino-N-(3-chlorophenyl)-4-(1,4-diazepan-1-yl)benzenesulfonamide hydrochloride

3-amino-N-(2-chlorophenyl)-4-(1,4-diazepan-1-yl)benzenesulfonamide hydrochloride

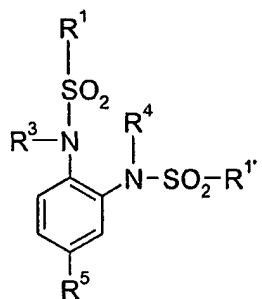
3-amino-4-(4-methyl-1,4-diazepan-1-yl)-N-phenylbenzenesulfonamide hydrochloride

3-amino-N-(2-methoxyphenyl)-4-(1-piperazinyl)benzenesulfonamide hydrochloride

20 2-[1,4]Diazepan-1-yl-5-(3,4-dihydro-1H-isoquinoline-2-sulfonyl)-aniline dihydrochloride

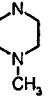
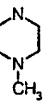
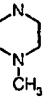
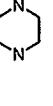
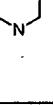
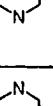
hydrochloride

3-Amino-2-chloro-N-naphthalen-1-yl-4-piperazin-1-yl-benzenesulfonamide, hydrochloride hydrochloride

**TABLE I**Compounds of the formula I wherein R<sup>2</sup> is -SO<sub>2</sub>-R<sup>1'</sup>

5

	Name	R <sup>1</sup>	R <sup>1'</sup>	R <sup>3</sup>	R <sup>4</sup>	R <sup>5</sup>
1	N-[2-{ethyl[(3-fluorophenyl)sulfonyl]amino}-4-(4-methyl-1-piperazinyl)phenyl]-3-fluorobenzenesulfonamide			H	Et	
2	N-[2-{ethyl(phenylsulfonyl)amino}-4-(4-methyl-1-piperazinyl)phenyl]benzenesulfonamide			H	Et	
3	3-fluoro-N-[2-{[(3-fluorophenyl)sulfonyl]amino}-4-(4-methyl-1-piperazinyl)phenyl]benzenesulfonamide			H	H	
4	N-{4-(4-methyl-1-piperazinyl)-2-[(8-quinolinylsulfonyl)amino]phenyl}-8-quinolinesulfonamide hydrochloride			H	H	
5	N-[2-chloro-4-({4-(4-methyl-1-piperazinyl)-2-[(phenylsulfonyl)amino]anilino}sulfonyl)phenyl]acetamide			H	H	
6	3,4-dimethoxy-N-{4-(4-methyl-1-piperazinyl)-2-[(phenylsulfonyl)amino]phenyl}benzenesulfonamide			H	H	

	Name	R <sup>1</sup>	R <sup>1'</sup>	R <sup>3</sup>	R <sup>4</sup>	R <sup>5</sup>
7	3-methoxy-4-methyl-N-{4-(4-methyl-1-piperazinyl)-2-[(phenylsulfonyl)amino]phenyl}benzenesulfonamide			H	H	
8	4-methyl-N-{4-(4-methyl-1-piperazinyl)-2-[(methylsulfonyl)amino]phenyl}benzenesulfonamide		-CH <sub>3</sub>	H	H	
9	3,4-dimethoxy-N-{4-(4-methyl-1-piperazinyl)-2-[(methylsulfonyl)amino]phenyl}benzenesulfonamide		-CH <sub>3</sub>	H	H	
10	3-cyano-N-{4-(4-methyl-1-piperazinyl)-2-[(methylsulfonyl)amino]phenyl}benzenesulfonamide		-CH <sub>3</sub>	H	H	
11	N-{4-(1-piperazinyl)-2-[(phenylsulfonyl)amino]phenyl}-1-naphthalenesulfonamide			H	H	
12	5-(dimethylamino)-N-{4-(1-piperazinyl)-2-[(phenylsulfonyl)amino]phenyl}-1-naphthalenesulfonamide			H	H	
13	N-[2-[(phenylsulfonyl)amino]-4-(1-piperazinyl)phenyl]-8-quinolinesulfonamide			H	H	
14	2,4,6-trimethyl-N-{2-[(phenylsulfonyl)amino]-4-(1-piperazinyl)phenyl}benzenesulfonamide			H	H	
15	4-methyl-N-[2-[(phenylsulfonyl)amino]-4-(1-piperazinyl)phenyl]benzenesulfonamide			H	H	
16	N-[2-({[(E)-2-phenylethyl]sulfonyl}amino)-5-(1-piperazinyl)phenyl]benzenesulfonamide			H	H	

	Name	R <sup>1</sup>	R <sup>1'</sup>	R <sup>3</sup>	R <sup>4</sup>	R <sup>5</sup>
17	2,5-dimethoxy-N-[2-[(phenylsulfonyl)amino]-4-(1-piperazinyl)phenyl]benzenesulfonamide			H	H	
18	2-methyl-N-[2-[(phenylsulfonyl)amino]-4-(1-piperazinyl)phenyl]benzenesulfonamide			H	H	
19	2,4-difluoro-N-[2-[(phenylsulfonyl)amino]-4-(1-piperazinyl)phenyl]benzenesulfonamide			H	H	
20	4-butoxy-N-[2-[(phenylsulfonyl)amino]-4-(1-piperazinyl)phenyl]benzenesulfonamide			H	H	
21	3,5-dimethyl-N-[2-[(phenylsulfonyl)amino]-4-(1-piperazinyl)phenyl]-4-isoxazolesulfonamide			H	H	
22	5-fluoro-2-methyl-N-[2-[(phenylsulfonyl)amino]-4-(1-piperazinyl)phenyl]benzenesulfonamide			H	H	
23	4-(methylsulfonyl)-N-[2-[(phenylsulfonyl)amino]-4-(1-piperazinyl)phenyl]benzenesulfonamide			H	H	
24	2-(methylsulfonyl)-N-[2-[(phenylsulfonyl)amino]-4-(1-piperazinyl)phenyl]benzenesulfonamide			H	H	
25	2-methoxy-4-methyl-N-[2-[(phenylsulfonyl)amino]-4-(1-piperazinyl)phenyl]benzenesulfonamide			H	H	
26	4-methoxy-2-methyl-N-[2-[(phenylsulfonyl)amino]-4-(1-piperazinyl)phenyl]benzenesulfonamide			H	H	

27	N-{4-(1,4-diazepan-1-yl)-2-[(phenylsulfonyl)amino]phenyl}benzenesulfonamide			H	H	
28	N-(4-(1,4-diazepan-1-yl)-2-{[(3-fluorophenyl)sulfonyl]amino}phenyl)-3-fluorobenzenesulfonamide			H	H	
29	N-{5-(1,4-diazepan-1-yl)-2-[(phenylsulfonyl)amino]phenyl}-N-ethylbenzenesulfonamide			H	Et	
30	N-{5-(1,4-diazepan-1-yl)-2-[(methylsulfonyl)amino]phenyl}benzenesulfonamide	Me		H	H	
31	N-{5-(1,4-diazepan-1-yl)-2-[(ethylsulfonyl)amino]phenyl}benzenesulfonamide	Et		H	H	
32	N-{4-(1,4-diazepan-1-yl)-2-[(phenylsulfonyl)amino]phenyl}[1,1'-biphenyl]-4-sulfonamide			H	H	
33	N-{4-(1,4-diazepan-1-yl)-2-[(phenylsulfonyl)amino]phenyl}-2,1,3-benzoxadiazole-4-sulfonamide			H	H	
34	N-{4-(1,4-diazepan-1-yl)-2-[(phenylsulfonyl)amino]phenyl}-2-naphthalenesulfonamide			H	H	
35	N-{4-(1,4-diazepan-1-yl)-2-[(methylsulfonyl)amino]phenyl}benzenesulfonamide		Me	H	H	
36	N-{4-(1,4-diazepan-1-yl)-2-[methyl(methylsulfonyl)amino]phenyl}benzenesulfonamide PHA-526210A		Me	H	Me	

37	N-{4-(1,4-diazepan-1-yl)-2-[(methylsulfonyl)amino]phenyl}-N-methylbenzenesulfonamide		Me	Me	H	
38	N-{4-(1,4-diazepan-1-yl)-2-[methyl(phenoxy)sulfonyl]amino}phenyl benzenesulfonamide			H	Me	
39	N-{4-(1,4-diazepan-1-yl)-2-[(methylsulfonyl)amino]phenyl}-1-naphthalenesulfonamide		Me	H	H	
40	N-{4-(1,4-diazepan-1-yl)-2-[(methylsulfonyl)amino]phenyl}-2-naphthalenesulfonamide		Me	H	H	
41	N-{4-(1,4-diazepan-1-yl)-2-[(methylsulfonyl)amino]phenyl}-4-fluorobenzenesulfonamide		Me	H	H	
42	N-{4-(1,4-diazepan-1-yl)-2-[(methylsulfonyl)amino]phenyl}-4-nitrobenzenesulfonamide		Me	H	H	
43	N-{4-(1,4-diazepan-1-yl)-2-[(methylsulfonyl)amino]phenyl}-3-(trifluoromethyl)benzenesulfonamide		Me	H	H	
44	N-{4-(1,4-diazepan-1-yl)-2-[(methylsulfonyl)amino]phenyl}-2-methylbenzenesulfonamide		Me	H	H	
45	N-{4-(1,4-diazepan-1-yl)-2-[(methylsulfonyl)amino]phenyl}-4-(trifluoromethoxy)benzenesulfonamide		Me	H	H	
46	N-{4-(1,4-diazepan-1-yl)-2-[(methylsulfonyl)amino]phenyl}-3,5-dimethyl-4-isoxazolesulfonamide		Me	H	H	

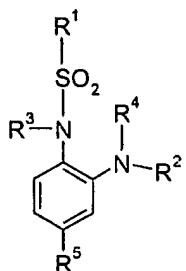
47	N-{4-(1,4-diazepan-1-yl)-2-[(methylsulfonyl)amino]phenyl}-3-methoxybenzenesulfonamide		Me	H	H	
48	N-{4-(1,4-diazepan-1-yl)-2-[(methylsulfonyl)amino]phenyl}-4-methylbenzenesulfonamide		Me	H	H	
49	N-{4-(1,4-diazepan-1-yl)-2-[ethyl(methylsulfonyl)amino]phenyl}-4-methylbenzenesulfonamide		Me	H	Et	
50	N-{4-(1,4-diazepan-1-yl)-2-[ethyl(methylsulfonyl)amino]phenyl}-3,4-dimethoxybenzenesulfonamide		Me	H	Et	
51	N-{4-(1,4-diazepan-1-yl)-2-[ethyl(methylsulfonyl)amino]phenyl}-7-quinolinesulfonamide		Me	H	Et	
52	N-{4-(1,4-diazepan-1-yl)-2-[methyl(methylsulfonyl)amino]phenyl}-4-methylbenzenesulfonamide		Me	H	Me	
53	N-{4-(1,4-diazepan-1-yl)-2-[methyl(methylsulfonyl)amino]phenyl}-1-naphthalenesulfonamide		Me	H	Me	
54	N-{4-(1,4-diazepan-1-yl)-2-[methyl(methylsulfonyl)amino]phenyl}-5-(2-pyridinyl)-2-thiophenesulfonamide		Me	H	Me	
55	N-{4-(1,4-diazepan-1-yl)-2-[(phenylsulfonyl)amino]phenyl}-1-naphthalenesulfonamide			H	H	
56	N-{4-(1,4-diazepan-1-yl)-2-[(phenylsulfonyl)amino]phenyl}-5-(dimethylamino)-1-naphthalenesulfonamide			H	H	

57	N-{4-(1,4-diazepan-1-yl)-2-[(phenylsulfonyl)amino]phenyl}-8-quinolinesulfonamide			H	H	
58	N-{4-(1,4-diazepan-1-yl)-2-[(phenylsulfonyl)amino]phenyl}-2,4,6-trimethylbenzenesulfonamide			H	H	
59	N-{4-(1,4-diazepan-1-yl)-2-[(phenylsulfonyl)amino]phenyl}-4-methylbenzenesulfonamide			H	H	
60	N-[5-(1,4-diazepan-1-yl)-2-({[(E)-2-phenylethenyl]sulfonyl}amino)phenyl]benzenesulfonamide			H	H	
61	N-{4-(1,4-diazepan-1-yl)-2-[(phenylsulfonyl)amino]phenyl}-2,5-dimethoxybenzenesulfonamide			H	H	
62	N-{4-(1,4-diazepan-1-yl)-2-[(phenylsulfonyl)amino]phenyl}-2-methylbenzenesulfonamide			H	H	
63	4-butoxy-N-{4-(1,4-diazepan-1-yl)-2-[(phenylsulfonyl)amino]phenyl}benzenesulfonamide			H	H	
63	N-{4-(1,4-diazepan-1-yl)-2-[(phenylsulfonyl)amino]phenyl}-3,5-dimethyl-4-isoxazolesulfonamide			H	H	
65	N-{4-(1,4-diazepan-1-yl)-2-[(phenylsulfonyl)amino]phenyl}-5-fluoro-2-methylbenzenesulfonamide			H	H	
66	N-{4-(1,4-diazepan-1-yl)-2-[(phenylsulfonyl)amino]phenyl}-4-(methylsulfonyl)benzenesulfonamide			H	H	
67	N-{4-(1,4-diazepan-1-yl)-2-[(methylsulfonyl)amino]phenyl}-N-methylbenzenesulfonamide			Me	Me	

68	N-{5-(1,4-diazepan-1-yl)-2-[methyl(phenylsulfonyl)amino]phenyl}-4-methylbenzenesulfonamide			Me	H	
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TABLE II

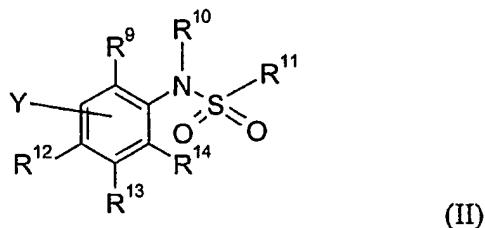
Compounds of the formula Ia



	Name	R <sup>1</sup>	R <sup>3</sup>	R <sup>2</sup>	R <sup>4</sup>	R <sup>5</sup>
69	N-[2-amino-4-(1-piperazinyl)phenyl]-3-fluorobenzenesulfonamide		H	H	H	
70	N-[2-(ethylamino)-4-(1-piperazinyl)phenyl]-3-fluorobenzenesulfonamide		H	H	Et	

*Compounds of the Formula II*

In a further aspect, the invention provides a compound having the general formula (II)



5

or a pharmaceutically acceptable salt thereof, wherein

R<sup>9</sup>, R<sup>12</sup> and R<sup>14</sup> are H; or

10 two of R<sup>9</sup>, R<sup>12</sup> and R<sup>14</sup> are H; and the remaining of R<sup>9</sup>, R<sup>12</sup> and R<sup>14</sup> is

(a) -NH<sub>2</sub>,

(b) -NHR<sup>6</sup>,

(c) -NR<sup>6</sup>R<sup>7</sup>,

(d) -N(CO)R<sup>6</sup>,

15 (e) -N(CS)R<sup>6</sup>, or

(f) -NO<sub>2</sub>;

R<sup>10</sup> and R<sup>11</sup> is a group R<sup>3</sup> or R<sup>1</sup> as defined for Formula I;

20 R<sup>13</sup> is

(a) homopiperazine,

(b) methylhomopiperazine or

(c) a group R<sup>5</sup> as defined for Formula I, wherein R<sup>8</sup> is as defined for Formula I;

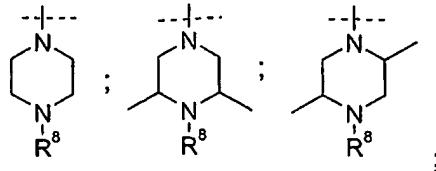
25 Y is as defined for Formula I.

Preferred compounds of the general formula (II) are those wherein:

R<sup>13</sup> is

- (a) homopiperazine,
- (b) methylhomopiperazine, or

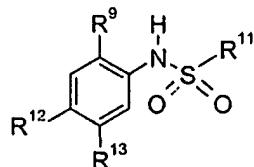
5     (c) a group R<sup>5</sup> selected from



R<sup>8</sup> is

- (a) H, or
- 10   (b) C<sub>1-6</sub> alkyl, in particular methyl;

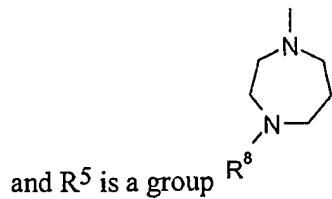
TABLE III

Compounds of the formula II wherein R<sup>10</sup>, R<sup>14</sup> and Y are H

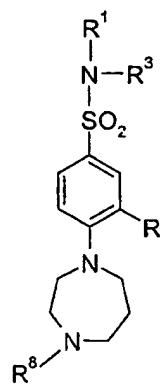
5

	Name	R <sup>9</sup>	R <sup>11</sup>	R <sup>12</sup>	R <sup>13</sup>
71	4-chloro-N-[5-(4-methyl-1,4-diazepan-1-yl)-2-nitrophenyl]benzenesulfonamide	-NO <sub>2</sub>		H	
72	N-[2-amino-5-(1,4-diazepan-1-yl)phenyl]benzenesulfonamide	-NH <sub>2</sub>		H	
73	N-[2-amino-5-(4-methyl-1,4-diazepan-1-yl)phenyl]benzenesulfonamide	-NH <sub>2</sub>		H	
74	N-[4-nitro-3-(1-piperazinyl)phenyl]benzenesulfonamide	H		-NO <sub>2</sub>	
75	N-[4-amino-3-(1-piperazinyl)phenyl]benzenesulfonamide	H		-NH <sub>2</sub>	

TABLE IV

Compounds wherein Y and group -N-R<sup>2</sup>R<sup>4</sup>, is assigned as group R in the following structure

10



	Name	R <sup>1</sup>	R <sup>3</sup>	-R	R <sup>8</sup>
76	3-amino-4-(1,4-diazepan-1-yl)-N-(4-methoxyphenyl)benzenesulfonamide		H	-NH <sub>2</sub>	H
77	3-amino-4-(1,4-diazepan-1-yl)-N-(3-methoxyphenyl)benzenesulfonamide		H	-NH <sub>2</sub>	H
78	3-amino-4-(1,4-diazepan-1-yl)-N-(2-methoxyphenyl)benzenesulfonamide		H	-NH <sub>2</sub>	H
79	3-amino-4-(1,4-diazepan-1-yl)-N-(3-fluorophenyl)benzenesulfonamide		H	-NH <sub>2</sub>	H
80	3-amino-4-(1,4-diazepan-1-yl)-N-methyl-N-phenylbenzenesulfonamide		-CH <sub>3</sub>	-NH <sub>2</sub>	H
81	3-amino-4-(1,4-diazepan-1-yl)-N-(4-isopropylphenyl)benzenesulfonamide		H	-NH <sub>2</sub>	H
82	3-amino-4-(1,4-diazepan-1-yl)-N-(4-methylphenyl)benzenesulfonamide		H	-NH <sub>2</sub>	H

	Name	R <sup>1</sup>	R <sup>3</sup>	-R	R <sup>8</sup>
83	3-amino-4-(1,4-diazepan-1-yl)-N-(2,5-dimethylphenyl)benzenesulfonamide		H	-NH <sub>2</sub>	H
84	3-amino-N-(3-chlorophenyl)-4-(1,4-diazepan-1-yl)benzenesulfonamide		H	-NH <sub>2</sub>	H
85	3-amino-N-(2-chlorophenyl)-4-(1,4-diazepan-1-yl)benzenesulfonamide		H	-NH <sub>2</sub>	H
86	3-amino-N-(2,4-dichlorophenyl)-4-(1,4-diazepan-1-yl)benzenesulfonamide		H	-NH <sub>2</sub>	H
87	3-amino-N-(2-methyl-5-chloro-phenyl)-4-(1,4-diazepan-1-yl)benzenesulfonamide		H	-NH <sub>2</sub>	H
88	3-amino-N-(2-methyl-3-chloro-phenyl)-4-(1,4-diazepan-1-yl)benzenesulfonamide		H	-NH <sub>2</sub>	H
89	3-amino-N-(4-trifluoro-phenyl)-4-(1,4-diazepan-1-yl)benzenesulfonamide		H	-NH <sub>2</sub>	H
90	3-amino-N-(4-fluorophenyl)-4-(1,4-diazepan-1-yl)benzenesulfonamide		H	-NH <sub>2</sub>	H
91	3-amino-N-(2-fluorophenyl)-4-(1,4-diazepan-1-yl)benzenesulfonamide		H	-NH <sub>2</sub>	H
92	3-amino-4-(4-methyl-1,4-diazepan-1-yl)-N-phenylbenzenesulfonamide		H	-NH <sub>2</sub>	-CH <sub>3</sub>
93	4-(1,4-diazepan-1-yl)-3-nitro-N-phenylbenzenesulfonamide		H	-NO <sub>2</sub>	H
94	3-amino-4-(1,4-diazepan-1-yl)-N-phenylbenzenesulfonamide		H	-NH <sub>2</sub>	H

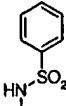
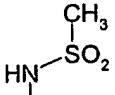
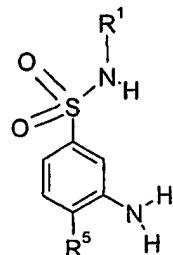
	Name	R <sup>1</sup>	R <sup>3</sup>	-R	R <sup>8</sup>
95	2-(1,4-diazepan-1-yl)-5-(4-morpholinylsulfonyl)phenylamine			-NH <sub>2</sub>	H
96	4-(1,4-diazepan-1-yl)-N-phenyl-3-[(phenylsulfonyl)amino]benzenesulfonamide		H		H
97	4-(1,4-diazepan-1-yl)-N-phenyl-3-[(methylsulfonyl)amino]benzenesulfonamide		H		H

TABLE V

Compounds wherein Y, R<sup>3</sup>, R<sup>2</sup> and R<sup>4</sup> are H

	Name	R <sup>1</sup>	R <sup>5</sup>
98	3-amino-N-(3-chlorophenyl)-4-(4-methyl-1-piperazinyl)benzenesulfonamide		
99	3-amino-N-(2-methoxyphenyl)-4-(4-methyl-1-piperazinyl)benzenesulfonamide		
100	3-amino-N-(2-methoxyphenyl)-4-(1-piperazinyl)benzenesulfonamide		
101	3-amino-N-(2-methoxyphenyl)-4-(3-methyl-1-piperazinyl)benzenesulfonamide		
102	3-Amino-4-(hexahydro-pyrrolo[1,2-a]pyrazin-2-yl)-N-(2-methoxyphenyl)benzenesulfonamide		
103	3-Amino-N-phenyl-4-piperazin-1-yl-benzenesulfonamide hydrochloride		
104	3-Amino-4-(3-methyl-piperazin-1-yl)-N-phenyl-benzenesulfonamide hydrochloride		
105	3-Amino-4-(4-ethyl-piperazin-1-yl)-N-phenyl-benzenesulfonamide hydrochloride		

	Name	R <sup>1</sup>	R <sup>5</sup>
106	3-Amino-4-(hexahydro-pyrrolo[1,2-a]pyrazin-2-yl)-N-phenylbenzenesulfonamide hydrochloride		
107	3-Amino-4-(5-methyl-2,5-diaza-bicyclo[2.2.1]hept-2-yl)-N-phenylbenzenesulfonamide hydrochloride		
108	3-Amino-4-(trans -2,5-dimethyl-piperazin-1-yl)-N-(2methoxy-phenyl)benzenesulfonamide hydrochloride		
109	2-(3-Amino-4-[1,4]diazepan-1-yl-benzenesulfonyl)-benzamide diacetic acid		
110	4-[4-(3-Fluoro-2-methoxy-phenylsulfamoyl)-2-amino-phenyl]-[1,4]diazepane ditrifluoroacetic acid		
111	2-[1,4]Diazepan-1-yl-5-(3,4-dihydro-1H-isoquinoline-2-sulfonyl)-aniline dihydrochloride		
112	4-[4-(3,4-Dihydro-2H-quinoline-1-sulfonyl)-2-amino-phenyl]-[1,4]diazepane ditrifluoroacetic acid		

TALBE VI



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	Name	R <sup>1</sup>	R <sup>5</sup>

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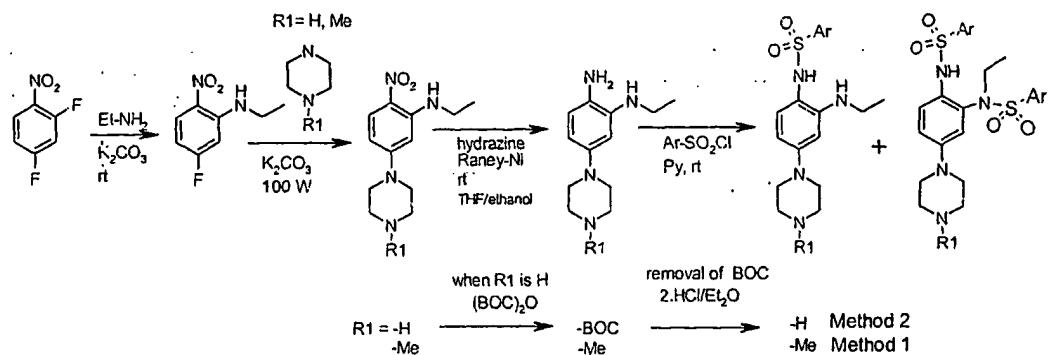
113	3-Amino-2-chloro-N-naphthalen-1-yl-4-piperazin-1-yl-benzenesulfonamide, hydrochloride		
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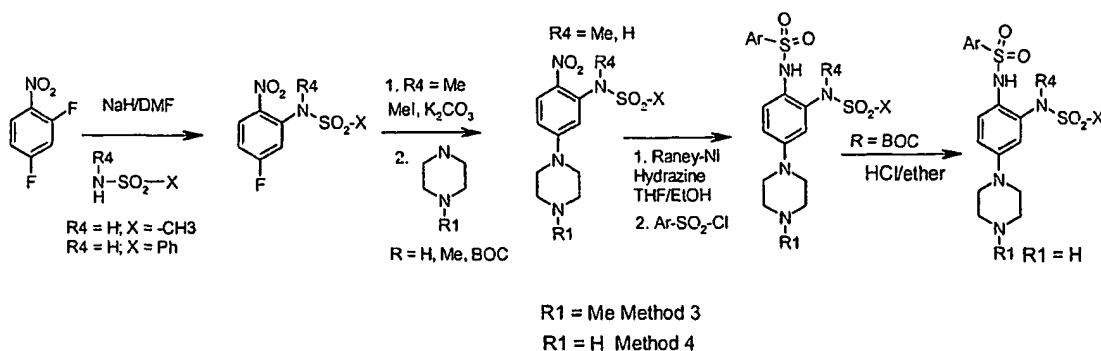
The compounds in the tables are hydrochloride salts, reported if otherwise

### 5 Processes for preparation

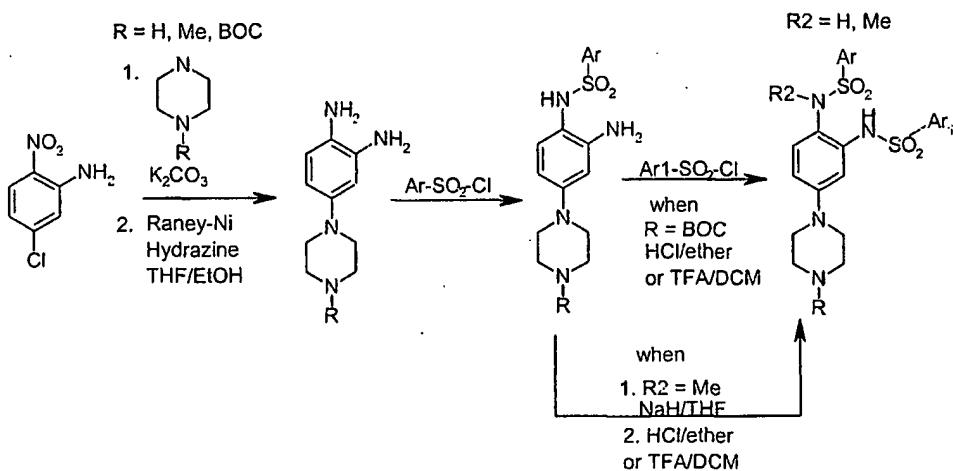
The compounds according to the invention having two sulfonyl groups were prepared according to the methods outlined in Schemes 1, 2 and 3.

#### 10 Scheme 1



**Scheme 2**

5

**Scheme 3**

10

Depending on the process conditions the end products of the Formula I are obtained either in neutral or salt form. Both the free base and the salts of these end products are within the scope of the invention.

15

Acid addition salts of the new compounds may in a manner known *per se* be transformed into the free base using basic agents such as alkali or by ion exchange. The free base obtained may also form salts with organic or inorganic acids.

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In the preparation of acid addition salts, preferably such acids are used which form suitably therapeutically acceptable salts. Examples of such acids are hydrohalogen acids, sulfuric acid, phosphoric acid, nitric acid, aliphatic, alicyclic, aromatic or heterocyclic carboxyl or sulfonic acids, such as formic acid, acetic acid, propionic acid, succinic acid, 5 glycolic acid, lactic acid, malic acid, tartaric acid, citric acid, ascorbic acid, maleic acid, hydroxymaleic acid, pyruvic acid, p-hydroxybensoic acid, embonic acid, methanesulfonic acid, ethanesulfonic acid, hydroxyethanesulfonic acid, halogenbensenenesulfonic acid, toluenesulfonic acid, mandelic acid or naphthalenesulfonic acid.

10 Throughout the specification and the appended claims, a given chemical formula or name shall encompass all stereo and optical isomers and racemates thereof where such isomers exist. All diastereomeric forms possible (pure enantiomers, tautomers, racemic mixtures and unequal mixtures of two enantiomers) are within the scope of the invention. Such compounds can also occur as cis- or trans-, E- or Z- double bond isomer forms. All 15 isomeric forms are contemplated.

*Pharmaceutical formulations*

20 Pharmaceutical formulations are usually prepared by mixing the active substance, or a pharmaceutically acceptable salt thereof, with conventional pharmaceutical excipients. The formulations can be further prepared by known methods such as granulation, compression, microencapsulation, spray coating, etc.

25 This invention relates to a method of treating obesity or type II diabetes. The method includes administering to a mammal subject (e.g., human) in need thereof an effective amount of one or more compounds of the formula (I) or the formula (II) above. Also within the scope of this invention is a method for modulating (e.g., inhibiting) 5-HT<sub>6</sub> receptor activity. The method includes administering to a mammal in need thereof an effective amount of a compound of the formula (I) or the formula (II) above.

30

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"An effective amount" refers to an amount of a compound which confers a therapeutic effect on the treated subject. The therapeutic effect may be objective (i.e., measurable by some test or marker) or subjective (i.e., subject gives an indication of or feels an effect). For clinical use, the compounds of the invention are formulated into 5 pharmaceutical formulations for oral, rectal, parenteral or other mode of administration. Usually the amount of active compounds is between 0.1-95% by weight of the preparation, preferably between 0.2-20% by weight in preparations for parenteral use and preferably between 1 and 50% by weight in preparations for oral administration.

10 The typical daily dose of the active substance varies within a wide range and will depend on various factors such as for example the individual requirement of each patient and the route of administration. In general, oral and parenteral dosages will be in the range of 5 to 1000 mg per day of active substance, preferably 50 to 150 mg per day.

15 The specific examples below are to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever. Without further elaboration, it is believed that one skilled in the art can, based on the description herein, utilize the present invention to its fullest extent. All publications cited herein are hereby incorporated by reference in their entirety.

20

## EXAMPLES

In the following examples, the structure of the prepared compounds were confirmed by standard spectroscopic methods and elemental analysis and/or high resolution MS. The 25 NMR data were obtained on a JEOL JNM-EX 270, a Bruker 400 DPX or a Bruker DRX 500 spectrometer. IR spectra were obtained on a Perkin Elmer SPECTRUM 1000 FT-IR spectrometer. High resolution MS were obtained on a Micromass LCT spectrometer. Elemental analysis was performed by Mikro Kemi AB Uppsala Sweden. Melting points, when given, were obtained on a Büchi or a Gallenkamp melting point apparatus and are 30 uncorrected.

**Synthesis according to Scheme 1, Method 2 (R = Boc)****INTERMEDIATE 1****5      Synthesis of N-Ethyl-5-fluoro-2-nitroaniline.**

A suspension of 2,4-difluoro-1-nitrobenzene (0.50 g, 0.003 mmol), ethylamine hydrochloride (0.49 g, 0.006 mmol), K<sub>2</sub>CO<sub>3</sub> (1.66 g, 0.012 mmol) in acetonitrile (30 mL) was stirred at room temperature for 16 hours and then filtered. The filtrate was concentrated and dissolved in small amount of CHCl<sub>3</sub>. Purification by column chromatography on silica using pentane/diethyl ether 95:5 as eluent gave 0.45 g of a yellow solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 8.23-8.18 (m, 1H), 8.08 (br s, 1H), 6.49-6.45 (m, 1H), 6.38-6.32 (m, 1H), 3.34-3.27 (m, 2H), 1.38 (tr, J = 7.22 Hz, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 167.55 (d, J<sub>CF</sub> = 255.6 Hz), 147.4 (d, J<sub>CF</sub> = 12.9 Hz), 129.91 (d, J<sub>CF</sub> = 12.9 Hz), 128.71 (br s), 103.73 (d, J<sub>CF</sub> = 24.8 Hz), 99.14 (d, J<sub>CF</sub> = 27.6 Hz), 37.88, 14.05; MS (posESI) m/z = found 184.0653, calc 184.0648. Anal. (C<sub>12</sub>H<sub>18</sub>N<sub>4</sub>O<sub>2</sub>) C, H, N.

**INTERMEDIATE 2****Synthesis of N-Ethyl-2-nitro-5-(1-piperazinyl)aniline.**

20      A suspension of N-ethyl-5-fluoro-2-nitroaniline (1.5 g, 8.12 mmol), piperazine (0.979 g, 11.37 mmol), K<sub>2</sub>CO<sub>3</sub> (3.36 g, 24.3 mmol) in DMF (40 mL) was heated in a microwave oven for 1 min at 100 W. The reaction mixture was allowed to cool and then heated for another minute at 100w. This procedure was repeated 5 times. The suspension was filtered and then concentrated. The crude oil was purified via flash chromatography on silica using CHCl<sub>3</sub>/MeOH/NH<sub>3</sub> 9:1:0.4% as eluent to give 1.53 g (75%) of a yellow solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 8.30 (br s, 1H), 8.08-8.04 (m, 1H), 6.25-6.20 (m, 1H), 5.88-5.86 (m, 1H), 3.39-3.28 (m, 6H), 3.03-2.97 (m, 4H), 1.37 (tr, J=7.2 Hz, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 156.27, 147.74, 128.96, 124.13, 104.28, 93.34, 48.22, 45.99, 37.73, 14.15; MS (posEI) m/z = 250 (M<sup>+</sup>); MS (posESI) m/z = found 250.1429, calc 250.1430. Anal. (C<sub>12</sub>H<sub>18</sub>N<sub>4</sub>O<sub>2</sub>) C,H,O.

30

**INTERMEDIATE 3**

**Synthesis of tert-Butyl 4-[3-(ethylamino)-4-nitrophenyl]-1-piperazinecarboxylate.**

To a solution of N-ethyl-2-nitro-5-(1-piperazinyl)aniline (1.020 g, 4.075 mmol), and NaOH (0.39 g, 2.45 mmol) in THF:H<sub>2</sub>O (64 mL, 1:1) was added a solution of di-tertbutyl-dicarbonate (2.67 g, 12.2 mmol) in 5 mL THF. The solution was stirred at room temperature for 16 hours. The mixture was neutralized with 1 N HCl. The volatiles were removed under vacuum to yield 1.4 g of crude material (98%). <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 8.28 (br s, 1H), 8.13-8.09 (m, 1H), 6.27-6.22 (m, 1H), 6.05-6.02 (m, 1H), 3.67-3.61 (m, 4H), 3.45-3.38 (m, 4H), 3.35-3.27 (m, 2H), 1.50 (s, 9H); MS (posESI) m/z = found 350.1951, calc 350.1954.

10

**INTERMEDIATE 4****Synthesis of tert-Butyl 4-[4-amino-3-(ethylamino)phenyl]-1-piperazinecarboxylate.**

To a solution of tert-butyl 4-[3-(ethylamino)-4-nitrophenyl]-1-piperazinecarboxylate (1.028 g, 2.93 mmol) in 40 mL EtOH:THF (4:1) solvent system was added Raney-Ni (1 mL of a EtOH suspension) followed by addition hydrazine hydrate (0.734 g, 14.67 mmol). The mixture was stirred vigorously for 3 hours and then filtered through a Celite pad pretreated with water. The filtrate was concentrated and then purified by column chromatography on silica using CHCl<sub>3</sub>/MeOH/NH<sub>3</sub> 9:1:0.4% as eluent to give 0.877 g (93%) of a red oil. The oil was used immediately in the next reaction. HPLC purity >90 %; MS (posEI) m/z = 320 (M<sup>+</sup>);

**Method 1, Scheme 1: General for sulfonylation (R1 = Me)****INTERMEDIATE 5**

25

**Synthesis of N-ethyl-5-(4-methyl-1-piperazinyl)-2-nitroaniline (Method 1, Scheme 1)**

N-ethyl-5-(4-methyl-1-piperazinyl)-2-nitroaniline was prepared from 2,4-difluoro-1-nitrobenzene and methylpiperazine using the same method described for N-ethyl-2-nitro-5-(1-piperazinyl)aniline and was obtained as yellow solid (99 %). <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 8.30 (br s, 1H), 8.08-8.04 (m, 1H), 6.25-6.20 (m, 1H), 5.89-5.86 (m, 1H), 3.45-3.39 (m, 4H), 3.35-3.25 (m, 2H), 2.56-2.50 (m, 4H), 2.35 (s, 3H), 1.37 (tr, J=7.2 Hz, 3)); <sup>13</sup>C NMR δ (CDCl<sub>3</sub>)

155.92, 147.72, 128.99, 124.19, 104.30, 94.37, 54.78, 47.05, 46.25, 37.73, 14.43; MS  
(posESI) m/z = found 264.1575, calc 264.1586. Anal. (C<sub>13</sub>H<sub>20</sub>N<sub>4</sub>O<sub>2</sub>·0.5 H<sub>2</sub>O) C, H, O.

## INTERMEDIATE 6

5

### Synthesis of N-2-Ethyl-4-(4-methyl-1-piperazinyl)-1,2-benzenediamine (Method 1, Scheme 1)

N-Ethyl-5-(4-methyl-1-piperazinyl)-2-nitroaniline was reduced with Raney-Ni as described previously for the synthesis of tert-butyl 4-[4-amino-3-(ethylamino)phenyl]-1-piperazinecarboxylate to give N-2-ethyl-4-(4-methyl-1-piperazinyl)-1,2-benzenediamine (yield >90%) as a red oil. The product is very sensitive to oxidation and was therefore used immediately in the next reaction step. HPLC purity >90 %; MS (posEI) m/z = 234 (M<sup>+</sup>);

## EXAMPLE 1

15

### N-[2-{Ethyl[(3-fluorophenyl)sulfonyl]amino}-4-(4-methyl-1-piperazinyl)phenyl]-3-fluorobenzenesulfonamide hydrochloride (Method 1, Scheme 1)

To a solution of amine N-2-ethyl-4-(4-methyl-1-piperazinyl)-1,2-benzenediamine (0.200 g, 0.853 mmol) and pyridine (0.48 mL, 5.97 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (8 mL) was added a solution of 3-fluorobenzenesulfonyl chloride (249 mg, 1.28 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2 mL). The mixture was stirred at room temperature for 16 hours. CH<sub>2</sub>Cl<sub>2</sub> (10 mL) was added and the mixture was washed with saturated aqueous NaHCO<sub>3</sub>. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. Purification by column chromatography (Al<sub>2</sub>O<sub>3</sub>, EtOAc/MeOH 9.5:0.5) gave two products. The first fraction contained 110 mg of N-[2-{ethyl[(3-fluorophenyl)sulfonyl]amino}-4-(4-methyl-1-piperazinyl)phenyl]-3-fluorobenzenesulfonamide hydrochloride. The second fraction contained 100 mg of N-[2-(ethylamino)-4-(4-methyl-1-piperazinyl)phenyl]-3-fluorobenzenesulfonamide hydrochloride. Both products were converted to the HCl-salts.

N-[2-{ethyl[(3-fluorophenyl)sulfonyl]amino}-4-(4-methyl-1-piperazinyl)phenyl]-3-fluorobenzenesulfonamide hydrochloride: <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ 11.14 (br s, 1H), 9.27 (s, 1H), 7.75-7.35 (m, 8H), 7.18-7.15 8m, 1H), 6.95-6.90 (m, 1H), 6.07-6.04 (m, 1H), 3.47-3.30

(m, 4H), 3.05-2.85 (m, 4H), 2.73 8d, J=4.7 Hz), 0.72 (tr, J=7.2Hz);  $^{13}\text{C}$  NMR (CD<sub>3</sub>OD)  $\delta$  162.65 (d, J<sub>CF</sub>=5.5 Hz), 160.68 (d, J<sub>CF</sub>=4.6 Hz), 146.61, 142.52 (d, J<sub>CF</sub>=7.4 Hz), 139.04 (d, J<sub>CF</sub>=6.4 Hz), 131.58 (131.63, 131.28, 128.67, 124.25, 123.14, 122.89, 120.56 (d, J<sub>CF</sub>=21 Hz), 120.05 (d, J<sub>CF</sub>=21 Hz), 116.52, 115.64, 114.80 (d, J<sub>CF</sub>=25Hz), 113.97 (d, J<sub>CF</sub>=25 Hz), 51.88, 5 45.82, 44.84, 41.79, 12.31; Ms (posES-FIA) *m/z* = 551 (M+H)

#### EXAMPLE 2

**N-[2-[ethyl(phenylsulfonyl)amino]-4-(4-methyl-1-piperazinyl)phenyl]-benzenesulfonamide hydrochloride (Scheme 1, Method 1)**

10 N-[2-[ethyl(phenylsulfonyl)amino]-4-(4-methyl-1-piperazinyl)phenyl]benzenesulfonamide hydrochloride was prepared as described in Scheme 1. Sulfonylation from N-2-ethyl-4-(4-methyl-1-piperazinyl)-1,2-benzenediamine and phenylsulfonyl chloride was performed as described in Method 1. Purification by chromatography (SiO<sub>2</sub>, chloroform:methanol:NH<sub>3</sub> 9:1:0.4%) followed by trituration with MeOH gave 68 mg (15% 15 yield) of the free base which was converted to its HCl-salt. MS (posES-FIA) *m/z* = found: 514.1700, calc: 514.1708; Anal. (C<sub>25</sub>H<sub>30</sub>N<sub>4</sub>O<sub>4</sub>S<sub>2</sub>.2HCl) C, H, N.

#### EXAMPLE 3

20 **3-Fluoro-N-[2-{[(3-fluorophenyl)sulfonyl]amino}-4-(4-methyl-1-piperazinyl)phenyl]benzenesulfonamide hydrochloride (Scheme 3)**

*Synthesis of 2-Amino-5-(4-methyl-1-piperazinyl)aniline.* A mixture of 2-nitro-3-chloroaniline (4.47g, 25.9 mmol), methylpipеразине (3.1 g, 31 mmol) and K<sub>2</sub>CO<sub>3</sub> (5.41g, 39 mmol) in acetonitrile was stirred at 70 °C for 48 h. The mixture was filtered and purified by 25 column chromatography (SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>/MeOH/Heptane/NH<sub>3</sub> 4:1:5 x 0.2 %) to give 1.6 g of product (unreacted starting material was isolated):  $^1\text{H}$ -NMR  $\delta$  7.66-7.45 (m, 5H), 6.78 (d, 1H), 6.62 (d, 1H), 6.50 (dd, 1H), 3.39-3.35 (m, 4H), 3.02-2.99 (m, 4H); MS (posES-FIA) *m/z* 333.0 (M<sup>+</sup> + H). The product (1.06 g, 4.49 mmol) was dissolved in EtOH:THF (4:1). Raney-Ni and hydrazine (1.12 mL, 22 mmol) were added. The reaction was stirred at room 30 temperature for 3 h until the yellow color disappeared. Filtration through wet Celite pad, followed by removal of the solvent afforded 0.802 g of 2-amino-5-(4-methyl-1-

piperazinyl)aniline which was used without further purification in the next step. 3-Fluorobenzenesulfonyl chloride (0.133 g, 0.68 mmol) was added to a solution of 2-amino-5-(4-methyl-1-piperazinyl)aniline (0.141 g, 0.68 mmol) and pyridine (514 mL, 6.39 mmol) in CH<sub>2</sub>Cl<sub>2</sub>. After 1 h the mixture was washed with aq NaHCO<sub>3</sub> (10 %), dried (MgSO<sub>4</sub>) and the solvent was removed. Purification by chromatography (SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>/methanol/heptane, 4:1:5) gave 3-fluoro-N-[2-amino-4-(4-methyl-1-piperazinyl)-phenyl]benzenesulfonamide (0.140 g, 57 %). MS (posES-FIA) *m/z* = found: 365.2, calcd: 364.14; Anal. (C<sub>17</sub>H<sub>22</sub>ClFN<sub>4</sub>O<sub>2</sub>S·3H<sub>2</sub>O) C, H, N, S. The reaction produced a small amount of bis-sulfonylated compound 3-fluoro-N-[2-{(3-fluorophenyl)sulfonyl}amino]-4-(4-methyl-1-piperazinyl)-phenyl]benzenesulfonamide (0.010 g, 3 %). The products were transformed into their HCl-salt before analysis; MS (posES-FIA) *m/z* = found. 523.5, calcd: 522.12. Anal. (C<sub>23</sub>H<sub>25</sub>ClF<sub>2</sub>N<sub>4</sub>O<sub>4</sub>S<sub>2</sub>) C, H, N, S.

#### EXAMPLE 4

15

#### N-{4-(4-methyl-1-piperazinyl)-2-[(8-quinolinylsulfonyl)amino]phenyl}-8-quinolinesulfonamide hydrochloride (Scheme 3)

8-Quinolinesulfonyl chloride (0.185 g, 0.81 mmol) was added to a solution of 2-amino-5-(4-methyl-1-piperazinyl)aniline (0.168 g, 0.81 mmol) and pyridine (514 mL, 6.39 mmol) in CH<sub>2</sub>Cl<sub>2</sub>. After 1 h at room temperature the mixture was washed with aq NaHCO<sub>3</sub> (10 %), dried (MgSO<sub>4</sub>) and the solvent was removed. Purification by chromatography (SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>/MeOH/heptane, 4:1:5) gave N-2-amino-4-(4-methyl-1-piperazinyl)-]-phenyl-8-quinolinesulfonamide (0.110 g, 35 %). MS (posES-FIA) *m/z* = found: 384.2, calcd 383.48; %); Anal. (C<sub>19</sub>H<sub>22</sub>ClN<sub>5</sub>O<sub>2</sub>S·3H<sub>2</sub>O) C, H, N, S and a small amount of the bis-sulfonylated N-{4-(4-methyl-1-piperazinyl)-2-[(8-quinolinylsulfonyl)amino]phenyl}-8-quinolinesulfonamide (0.070 g, 15 %). The product was converted to HCl salt before analysis; MS (posES-FIA) *m/z* = found: 589.6, calcd: 588.16; Anal. (C<sub>29</sub>H<sub>29</sub>ClN<sub>6</sub>O<sub>4</sub>S<sub>2</sub>·2H<sub>2</sub>O) C, H, N.

30 **Synthesis according to Scheme 2****Scheme 2, Method 3: General R1 = Me**

## INTERMEDIATE 7

### Synthesis of N-(5-fluoro-2-nitrophenyl)benzenesulfonamide (Scheme 2, Method 3)

5 Benzenesulfonamide (3.14 g, 20 mmol) was dissolved in DMF (100 mL) and NaH (60% in oil, 40 mmol, 1.60 g) was added. The reaction was stirred until the gas evolution ceased. 2,4-Difluoronitrobenzene (18 mmol, 2.9 g, 2 mL) was added and the reaction mixture was stirred over night at 35°C. The reaction mixture was poured into HCl (1M aq, 100 mL) and extracted with toluene (25 mL x 5). The organic phase was dried ( $\text{MgSO}_4$ ) and concentrated and re-crystallized from EtOH to give a first crop of 3.75 g of a yellow solid. A second crop of 0.20 g was collected from the EtOH remains. Yield 3.95 g, 13.3 mmol (74%).  
10 MS (posES-FIA)  $m/z$  = found: 296; Calc: 296.0.

## INTERMEDIATE 8

15 **Synthesis of N-[5-(4-methyl-1-piperazinyl)-2-nitrophenyl]benzenesulfonamide (Scheme 2, Method 3)**

N-(5-fluoro-2-nitrophenyl)benzenesulfonamide (2 x 0.50 g, 1.688 mmol) was treated with N-methyl-piperazine (2 x 4.65 g, 45.6 mmol) and put in two pyrex tubes and sealed.  
20 Each tube was put in a LabWell MW-10 microwave oven for 2 min at 50W. The reaction mixtures were combined and poured into 0.5 M NaOH (aq) and extracted with  $\text{CH}_2\text{Cl}_2$ , dried ( $\text{MgSO}_4$ ) and concentrated to give 0.99 g, (2.63 mmol) in 78% yield as a yellow solid. Anal ( $\text{C}_{17}\text{H}_{20}\text{N}_4\text{O}_4\text{S}$ ) C, H, N, S; MS (posES-FIA)  $m/z$  = found: 377.4; Calcd: 376.12.

25 **EXAMPLE 5**

### N-[2-Chloro-4-({4-(4-methyl-1-piperazinyl)-2-[(phenylsulfonyl)amino]-anilino}sulfonyl)phenyl]acetamide hydrochloride (Scheme 2, Method 3)

N-[5-(4-Methyl-1-piperazinyl)-2-nitrophenyl]benzenesulfonamide (0.600 g, 1.59 mmol) was dissolved in THF (20 mL) followed by the addition of Raney-Ni (0.322 g, in ethanol) and hydrazine hydrate (0.100 g, 2.0 mmol). The reaction mixture was stirred for 1h,

filtered through Celite and concentrated. The residue was dissolved in pyridine (12 mL) and divided in 12 equal parts. To one part was added 3-chloro-4-N-acetamido-benzenesulfonylchloride (52 mg, 0.20 mmol). The reaction mixture was stirred over night, poured into petroleum ether to form a precipitate that was collected by centrifugation. The precipitate purified by column chromatography ( $\text{SiO}_2$ ,  $\text{CH}_2\text{Cl}_2/\text{MeOH}$  95:5 to 9:1). The pure product was dissolved in MeOH and treated with HCl/diethyl ether to give 9.6 mg, (12% yield). MS (posES-FIA)  $m/z$  = found: 578.4; Calcd: 577.12.

#### EXAMPLE 6

10

##### **3,4-Dimethoxy-N-{4-(4-methyl-1-piperazinyl)-2-[(phenylsulfonyl)-amino]phenyl}benzenesulfonamide hydrochloride (Scheme 2, Method 3)**

N-[5-(4-Methyl-1-piperazinyl)-2-nitrophenyl]benzenesulfonamide (0.600 g, 1.59 mmol) was dissolved in THF (20 mL) followed by the addition of Raney-Ni (0.322 g, in ethanol) and hydrazine hydrate (0.100 g, 2.0 mmol). The reaction mixture was stirred for 1h, filtered through Celite and concentrated. The residue was dissolved in pyridine (12 mL) and divided in 12 equal parts. To one part was added 3,4-dimethoxy-benzenesulfonylchloride (47 mg, 0.20 mmol). The reaction mixture was stirred overnight, poured into petroleum ether to form a precipitate that was collected by centrifugation. The precipitate was purified by column chromatography ( $\text{SiO}_2$ ,  $\text{CH}_2\text{Cl}_2/\text{MeOH}$  95:5 to 9:1). The pure product was dissolved in MeOH and treated with HCl/diethyl ether to give 34.5 mg, (45% yield). MS (posES-FIA)  $m/z$  = found: 547.4; Calcd: 546.16.

#### EXAMPLE 7

25

##### **3-Methoxy-4-methyl-N-{4-(4-methyl-1-piperazinyl)-2-[(phenylsulfonyl)-amino]phenyl}benzenesulfonamide hydrochloride (Scheme 2, Method 3)**

N-[5-(4-Methyl-1-piperazinyl)-2-nitrophenyl]benzenesulfonamide (0.600 g, 1.59 mmol) was dissolved in THF (20 mL) followed by the addition of Raney-Ni (0.322 g, in ethanol) and hydrazine hydrate (0.100 g, 2.0 mmol). The reaction mixture was stirred for 1h, filtered through Celite and concentrated. The residue was dissolved in pyridine (12 mL) and

divided in 12 equal parts. To one part was added 2-methoxy-4-methylbenzenesulfonylchloride (44 mg, 0.20 mmol). The reaction mixture was stirred overnight, poured into petroleum ether to form a precipitate that was collected by centrifugation. The precipitate was purified by column chromatography (SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>/MeOH 95:5 to 5:9:1). The pure product was dissolved in MeOH and treated with HCl/diethyl ether to give 21 mg, (28% yield). MS (posES-FIA) *m/z* = found: 530.1635; Calcd: 530.1658.

## INTERMEDIATE 9

### 10      **Synthesis of N-(5-fluoro-2-nitrophenyl)methanesulfonamide (Scheme 2, Method 3)**

Methylsulfonamide (2.421 g, 25.4 mmol) was dissolved in DMF (100 mL) and NaH (60% in oil, 1.00 g, 25 mmol) was added. The reaction stirred for 1 h and added to a stirred solution of 2,4-difluoronitrobenzene (4.372 g, 27.5 mmol) in DMF (20 mL). The reaction mixture was stirred for 2h, poured into a mixture (1:1) of brine and 1M HCl, and extracted with toluene. The organic phase was dried (MgSO<sub>4</sub>), and concentrated to give a solid that was crystallized from toluene / petroleum ether. The flask tipped over and some material was lost, to give 1.32 g, 5.64 mmol in 22% yield. MS (posES-FIA) *m/z* = found: 234; Calcd: 234.01; Anal (C<sub>7</sub>H<sub>7</sub>FN<sub>2</sub>O<sub>4</sub>S), C, H, N, S.

## 20      INTERMEDIATE 10

### **Synthesis of N-[5-(4-methyl-1-piperazinyl)-2-nitrophenyl]-methanesulfonamide (Scheme 2, Method 3).**

N-(5-fluoro-2-nitrophenyl)methanesulfonamide (1.33 g, 5.68 mmol) was dissolved in 25 DMF (10 mL) and N-methylpiperazine (2.00 g, 20 mmol) was added. The reaction mixture was stirred at 20°C for 1h, and then heated with a heat gun for 5 min to reach boiling of DMF (150°C), then left stirring for another hour. The reaction mixture was then poured into brine and extracted with toluene (10 mL x 2), EtOAc (20 mL x 2) and CH<sub>2</sub>Cl<sub>2</sub> (20 mL x 2), NaHCO<sub>3</sub> was then added to the water phase and then the water phase was extracted with 30 CH<sub>2</sub>Cl<sub>2</sub> (20 mL x 2). The organic phases were combined and dried (MgSO<sub>4</sub>) and concentrated to give a semi solid. EtOH was added and left over night and then filtered off to

give 1.503 g (4.78 mmol) in 84 % yield. MS (posES-FIA) *m/z* = found: 315; Calc M=314.10; Anal (C<sub>12</sub> H<sub>18</sub> N<sub>4</sub> O<sub>4</sub> S), C, H, N, S.

#### EXAMPLE 8

5

##### **4-Methyl-N-{4-(4-methyl-1-piperazinyl)-2-[(methylsulfonyl)amino]-phenyl}benzenesulfonamide hydrochloride (Scheme 2, Method 3)**

N-[5-(4-methyl-1-piperazinyl)-2-nitrophenyl]-methanesulfonamide (0.45 g, 1.43 mmol) was dissolved in THF (10 mL) followed by the addition of Raney-Ni (0.15 g in ethanol) and hydrazine hydrate (78 mg, 1.56 mmol). The reaction was stirred for 1h. Another aliquot of hydrazine hydrate (20  $\mu$ L) was added and the reaction stirred for another hour, filtered through Celite and concentrated to give 0.42 g that was used to the next step without further purification. The material was dissolved in DMF (10 mL) and divided into 3 equal parts. To one part was added *p*-toluene sulfonyl chloride (0.095 g, 0.5 mmol) and the reaction was stirred for 1 h and poured into a mixture of petroleum ether/acetone (30 mL/10 mL) to give a precipitate. Additional product was found in the solution and added to the precipitate. The product was isolated by chromatography (SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>/MeOH 9:1) to give 0.063 g, (28% yield). MS (posES-FIA) *m/z* = found: 38.1393; Calcd: 438.1395.

20    

#### EXAMPLE 9

##### **3,4-Dimethoxy-N-{4-(4-methyl-1-piperazinyl)-2-[(methylsulfonyl)amino]-phenyl}benzenesulfonamide hydrochloride (Scheme 2, Method 3)**

N-[5-(4-methyl-1-piperazinyl)-2-nitrophenyl]-methanesulfonamide (0.45 g, 1.43 mmol) was dissolved in THF (10 mL) and Raney-Ni (0.15 g in ethanol) was added followed by hydrazine hydrate (78 mg, 1.56 mmol) and the reaction was stirred for 1h. Additional hydrazine hydrate (20  $\mu$ L) was added and the reaction stirred for another hour, filtered through Celite and concentrated to give 0.42 g of product that was used without further purification. The material was dissolved in DMF (10 mL) and divided into 3 equal parts. To one part was added 3,4 dimethoxybenzenesulfonylchloride (0.118 g, 0.5 mmol) and the reaction was stirred for 1 h, poured into a mixture of petroleum ether/acetone (30 mL/10 mL)

to form a precipitate. Additional product was found in the solution and was added to the precipitate. The product was isolated by chromatography ( $\text{SiO}_2$ ,  $\text{CH}_2\text{Cl}_2/\text{MeOH}$  9:1) to give 0.064 g, (26% yield). MS (posES-FIA)  $m/z$  = found: 484.1436; Calcd: 484.1450.

#### EXAMPLE 10

5

#### 3-Cyano-N-{4-(4-methyl-1-piperazinyl)-2-[(methylsulfonyl)amino]-phenyl}benzenesulfonamide hydrochloride (Scheme 2, Method 3)

N-[5-(4-methyl-1-piperazinyl)-2-nitrophenyl]-methanesulfonamide (0.45 g, 1.43 mmol) was dissolved in THF (10 mL) and Rayney-Ni (0.15 g in ethanol) was added followed 10 by hydrazine hydrate (78 mg, 1.56 mmol) and the reaction was stirred for 1h. Additional hydrazine hydrate (20  $\mu\text{L}$ ) was added and the reaction stirred for another hour, filtered through Celite and concentrated to give 0.42 g of product that was used without further purifications. The material was dissolved in DMF (10 mL) and divided into 3 equal parts. To one part was added 3-cyanobenzenesulfonylchloride (0.101 g, 0.5 mmol) and the reaction 15 was stirred for 1 h. poured into a mixture of petroleum ether/acetone (30 mL/10 mL) to form a precipitate. Additional product was found in the solution and was combined to the precipitate. The product was isolated by chromatography ( $\text{SiO}_2$ ,  $\text{CH}_2\text{Cl}_2/\text{MeOH}$  9:1) to give 0.0301g, (13% yield). MS (posES-FIA)  $m/z$  = found: 449.1177; Calcd: 449.1191.

20 Scheme 2, Method 4: General R1 = H

#### N-(2-amino-5-(4-boc-1-piperazinyl)-phenyl)-benzenesulfonamide

A mixture of N-(2-nitro-3-fluorophenyl)-benzenesulfonamide (4.68 g, 15.7 mmol), Boc-piperazine (3.5 g, 18.9 mmol) and  $\text{K}_2\text{CO}_3$  (3.8 g, 27.8 mmol) in DMF was stirred at 70°C for 24h. The mixture was filtered and purified by column chromatography ( $\text{SiO}_2$ , 25  $\text{CH}_2\text{Cl}_2/\text{MeOH}/\text{heptane}/\text{NH}_3$  4:1:5:0.2 %) to give 2.0 g of desired product.  $^1\text{H-NMR}$   $\delta$  7.98 (d, 1H), 7.89-7.84 (m, 2H), 7.63-7.50 (m, 3H), 7.00 (d, 1H), 6.68 (dd, 1H), 3.59-3.45 (m, 8H), 1.49 (s, 9H); MS (posES-FIA)  $m/z$  = found: 485.0 ( $\text{M}^+ + \text{Na}^+$ ). The product (1.85 g, 4.00 mmol) was dissolved in EtOH:THF (4:1) followed by addition of Raney-Ni and hydrazine (1.0 mL, 20 mmol). The reaction was stirred at room temperature for 3 h until the 30 yellow color disappeared. Filtration through wet Celite, followed by removal of the solvent

afforded 1.26 g of N-(2-amino-5-(4-tert-butoxycarbonyl-1-piperazinyl)-phenyl)-benzenesulfonamide which was used without further purification.

To a solution of N-{2-amino-5-(4-*t*-butyloxycarbonyl-piperazinyl)-phenyl}benzenesulfonamide (79 mg, 0.184 mmol) and pyridine (131 µL, 1.6 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (7 mL) and different sulfonylchlorides (0.239 mmol) was added. After 2 h at room temperature the solvent was removed. Purification by chromatography (SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>/MeOH/heptane, 4:1:15) followed by Boc-deprotection which was achieved by dissolving the residue in small amount of MeOH and adding HCl/ether. The mixture was left at room temperature for 0.5 h after which the solvent was removed. Re-crystallization (MeOH/ether) afforded the final products respectively.

#### EXAMPLE 11

N-{4-(1-Piperazinyl)-2-[(phenylsulfonyl)amino]phenyl}-1-naphthalenesulfonamide hydrochloride (**Scheme 2, Method 4**)  
N-{4-(1-Piperazinyl)-2-[(phenylsulfonyl)amino]phenyl}-1-naphthalenesulfonamide was synthesized from N-{2-amino-5-(4-*t*-butyloxycarbonyl-piperazinyl)-phenyl}benzenesulfonamide and 1-naphthalenesulfonylchloride (54 mg, 0.239 mmol) according to general method 3 to give 40 mg of a purple solid. MS (posES-FIA) m/z = Found: 523.2; Calcd 523.14; <sup>1</sup>H NMR δ 8.83-8.59 (m, 1H), 8.10 (d, 1H), 8.02-7.97 (m, 1H), 7.90 (d, 1H), 7.74-7.38 (m, 8H), 6.69-6.65 (m, 1H), 6.39-6.34 (m, 2H), 3.35-3.14 (m, 8H).

#### EXAMPLE 12

5-(Dimethylamino)-N-{4-(1-piperazinyl)-2-[(phenylsulfonyl)amino]phenyl}-1-naphthalenesulfonamide hydrochloride (**Scheme 2, Method 4**)  
5-(Dimethylamino)-N-{4-(1-piperazinyl)-2-[(phenylsulfonyl)amino]phenyl}-1-naphthalenesulfonamide was synthesized from N-{2-amino-5-(4-*t*-butyloxycarbonyl-piperazinyl)-phenyl}benzenesulfonamide and dansylchloride (64 mg, 0.239 mmol) according to general method 3 to give 60 mg of a purple solid. MS (posES-FIA) m/z =

Found: 566.3; Calcd: 566.18;  $^1\text{H}$  NMR  $\delta$  8.84 (d, 1H), 8.60 (d, 1H), 8.08 (d, 2H), 7.84-7.47 (m, 7H), 6.70 (d, 1H), 6.56-6.53 (m, 1H), 6.41-6.37 (m, 1H), 3.46 (s, 6H), 3.25-3.12 (m, 8H).

### EXAMPLE 13

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#### **N-[2-[(Phenylsulfonyl)amino]-4-(1-piperazinyl)phenyl]-8-quinolinesulfonamide hydrochloride (Scheme 2, Method 4)**

N-[2-[(Phenylsulfonyl)amino]-4-(1-piperazinyl)phenyl]-8-quinolinesulfonamide was synthesized from N-{2-amino-5-(4-t-butyloxycarbonyl-piperazinyl)-phenyl}benzenesulfonamide and 8-quinolinesulfonylchloride (54 mg, 0.239 mmol) according to general method 3 to give 50 mg of a purple solid. MS (posES-FIA) m/z = Found: 524.2; Calcd: 524.13;  $^1\text{H}$  NMR  $\delta$  9.34 (dd, 1H), 8.79 (dd, 1H), 8.37 (dd, 1H), 8.25 (dd, 1H), 7.92 (dd, 1H), 7.73 (t, 1H), 7.57-7.40 (m, 5H), 7.17 (d, 1H), 6.71 (dd, 1H), 6.14 (d, 1H), 3.23-3.08 (m, 8H).

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### EXAMPLE 14

#### **2,4,6-Trimethyl-N-[2-[(phenylsulfonyl)amino]-4-(1-piperazinyl)phenyl]benzenesulfonamide hydrochloride (Scheme 2, Method 4)**

2,4,6-Trimethyl-N-[2-[(phenylsulfonyl)amino]-4-(1-piperazinyl)phenyl]benzenesulfonamide was synthesized from N-{2-amino-5-(4-t-butyloxycarbonyl-piperazinyl)-phenyl}benzenesulfonamide and 2-mesitylenesulfonylchloride (52 mg, 0.239 mmol) according to general method 3 to give 50 mg of a purple solid. MS (posES-FIA) m/z = Found: 515.3; Calcd 515.17;  $^1\text{H}$ -NMR  $\delta$  7.74 (d, 2H); 7.63-7.46 (m, 3H), 6.92 (s, 2H), 6.74-6.55 (m, 3H), 3.27-3.20 (m, 8H), 2.35 (s, 6H), 2.25 (s, 3H).

### EXAMPLE 15

#### **4-Methyl-N-[2-[(phenylsulfonyl)amino]-4-(1-piperazinyl)phenyl] benzenesulfonamide hydrochloride (Scheme 2, Method 4)**

4-Methyl-N-[2-[(phenylsulfonyl)amino]-4-(1-piperazinyl)phenyl]benzenesulfonamide was synthesized from N-{2-amino-5-(4-*t*-butyloxycarbonyl-piperazinyl)- phenyl}benzenesulfonamide and p-toluenesulfonylchloride (46 mg, 0.239 mmol) according to general method 3 to give 70 mg of a purple solid. MS (posES-FIA) m/z = Found: 487.2; Calcd: 487.14;  $^1\text{H-NMR}$   $\delta$  7.73-7.45 (m, 7H), 7.26 (d, 2H), 6.74 (s, 1H), 6.62-6.60 (m, 2H), 3.69 (app t, 2H), 3.39 (app t, 2H), 3.29-3.74 (m, 4H), 2.38 (s, 3H).

#### EXAMPLE 16

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#### N-[2-({[(E)-2-Phenylethenyl]sulfonyl}amino)-5-(1-piperazinyl)phenyl]benzenesulfonamide hydrochloride (Scheme 2, Method 4)

N-[2-({[(E)-2-Phenylethenyl]sulfonyl}amino)-5-(1-piperazinyl)phenyl]benzenesulfonamide was synthesized from N-{2-amino-5-(4-*t*-butyloxycarbonyl-piperazinyl)- phenyl}benzenesulfonamide and  $\beta$ -styrenesulfonylchloride (48 mg, 0.239 mmol) according to general method 3 to give before Boc-deprotection 160 mg of a purple solid. MS (posES-FIA) m/z = Found: 499.2; Calcd 499.14;  $^1\text{H-NMR}$   $\delta$  8.26 (d, 1H), 8.04 (d, 1H), 7.75-7.38 (m, 8H), 7.22 (d, 1H,  $J$  = 15.4 Hz), 7.16 (d, 1H), 6.97 (d, 1H,  $J$  = 15.4 Hz), 6.78 (dd, 1H), 6.68 (d, 1H), 3.68 (app t, 2H), 3.39 (app t, 2H), 3.28-3.21 (m, 4H).

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#### EXAMPLE 17

#### 2,5-Dimethoxy-N-[2-[(phenylsulfonyl)amino]-4-(1-piperazinyl)phenyl]benzenesulfonamide hydrochloride (Scheme 2, Method 4)

2,5-Dimethoxy-N-[2-[(phenylsulfonyl)amino]-4-(1-piperazinyl)phenyl]benzenesulfonamide was synthesized from of N-{2-amino-5-(4-*t*-butyloxycarbonyl-piperazinyl)- phenyl}benzenesulfonamide and 2,5-dimethoxybenzenesulfonylchloride (57 mg, 0.239 mmol) according to general method 3 to give 60 mg of a purple solid. MS (posES-FIA) m/z = Found: 533.1; Calcd: 533.14;  $^1\text{H-NMR}$   $\delta$  7.68-7.48 (m, 5H), 7.16-7.05 (m, 4H), 6.69 (dd, 1H), 6.42 (d, 1H), 4.03 (s, 3H), 3.69 (s, 3H), 3.26-3.10 (m, 8H).

**EXAMPLE 18****2-Methyl-N-[2-[(phenylsulfonyl)amino]-4-(1-piperazinyl)phenyl] benzenesulfonamide hydrochloride (Scheme 2, Method 4)**

5        2-Methyl-N-[2-[(phenylsulfonyl)amino]-4-(1-piperazinyl)phenyl]benzenesulfonamide was synthesized from N-{2-amino-5-(4-*t*-butyloxycarbonyl-piperazinyl)- phenyl}benzenesulfonamide and o-toluenesulfonylchloride (46 mg, 0.239 mmol) according to general method 3 to give before Boc-deprotection 160 mg of a purple solid. MS (posES-FIA) m/z = Found: 487.1; Calcd 487.14; <sup>1</sup>H-NMR δ 7.74-7.16  
10 (m, 8H), 6.78-6.52 (m, 4H), 3.27-3.16 (m, 8H), 2.58 (s, 3H).

**EXAMPLE 19**

15        **2,4-Difluoro-N-[2-[(phenylsulfonyl)amino]-4-(1-piperazinyl)phenyl] benzenesulfonamide hydrochloride (Scheme 2, Method 4)**  
2,4-Difluoro-N-[2-[(phenylsulfonyl)amino]-4-(1-piperazinyl)phenyl] benzenesulfonamide was synthesized from N-{2-amino-5-(4-*t*-butyloxycarbonyl-piperazinyl)- phenyl}benzenesulfonamide and 2,4-difluorobenzenesulfonylchloride (94 mg, 0.455 mmol) according to general method 3 to give before Boc-deprotection 160 mg of a  
20 purple solid. MS (posES-FIA) m/z = Found: 509.1; Calcd 509.11; <sup>1</sup>H-NMR δ 77.71-7.46 (m, 6H), 7.25-7.17 (m, 1H), 7.03-6.96 (m, 2H), 6.72 (dd, 1H), 6.44 (d, 1H), 3.20-3.16 (m, 8H).

**EXAMPLE 20**

25        **4-Butoxy-N-[2-[(phenylsulfonyl)amino]-4-(1-piperazinyl)phenyl] benzenesulfonamide hydrochloride (Scheme 2, Method 4)**  
4-Butoxy-N-[2-[(phenylsulfonyl)amino]-4-(1-piperazinyl)phenyl]benzenesulfonamide was synthesized from N-{2-amino-5-(4-*t*-butyloxycarbonyl-piperazinyl)- phenyl}benzenesulfonamide and 4-*n*-butoxybenzenesulfonylchloride (59 mg, 0.239 mmol) according to general method 3 to give

70 mg of a purple solid. MS (posES-FIA) m/z = Found: 545.2; Calcd 545.18;  $^1\text{H-NMR}$   $\delta$  7.73-7.45 (m, 7H), 6.95-6.91 (m, 2H), 6.72-6.70 (m, 1H), 4.00 (t, 2H), 3.29-3.24 (m, 8H), 1.79-1.70 (m, 2H), 1.55-1.43 (m, 2H), 0.97 (t, 3H).

5 EXAMPLE 21

**3,5-Dimethyl-N-[2-[(phenylsulfonyl)amino]-4-(1-piperazinyl)phenyl]-4-isoxazolesulfonamide hydrochloride (Scheme 2, Method 4)**

3,5-Dimethyl-N-[2-[(phenylsulfonyl)amino]-4-(1-piperazinyl)phenyl]-4-isoxazolesulfonamide was synthesized from N-{2-amino-5-(4-t-butyloxycarbonylpiperazinyl)-phenyl}benzenesulfonamide and 3,5-dimethylisoxazolesulfonylchloride (47 mg, 0.239 mmol) according to general method 3 to give 70 mg of a purple solid. MS (posES-FIA) m/z = Found: 492.1; Calcd 492.13;  $^1\text{H-NMR}$   $\delta$  7.72-7.47 (m, 5H), 6.98 (d, 1H), 6.80 (dd, 1H), 6.50 (d, 1H), 3.28-3.22 (m, 8H), 2.22 (s, 3H), 2.11 (s, 3H).

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EXAMPLE 22

**5-Fluoro-2-methyl-N-[2-[(phenylsulfonyl)amino]-4-(1-piperazinyl)phenyl]benzenesulfonamide (Scheme 2, Method 4)**

5-Fluoro-2-methyl-N-[2-[(phenylsulfonyl)amino]-4-(1-piperazinyl)-phenyl]benzenesulfonamide was synthesized from N-{2-amino-5-(4-t-butyloxycarbonylpiperazinyl)-phenyl}benzenesulfonamide and 5-fluoro-2-methylbenzenesulfonylchloride (50 mg, 0.239 mmol) according to general method 3 to give 60 mg of a purple solid. MS (posES-FIA) m/z = Found: 505.2; Calcd 505.13;  $^1\text{H-NMR}$   $\delta$  7.73-7.17 (m, 8H), 6.83 (d, 1H), 6.68 (dd, 1H), 6.50 (dd, 1H), 3.27-3.17 (m, 8H), 2.55 (s, 3H).

EXAMPLE 23

**4-(Methylsulfonyl)-N-[2-[(phenylsulfonyl)amino]-4-(1-piperazinyl)phenyl]-benzenesulfonamide hydrochloride (Scheme 2, Method 4)**

4-(Methylsulfonyl)-N-[2-[(phenylsulfonyl)amino]-4-(1-piperazinyl)-phenyl]benzenesulfonamide was synthesized from N-{2-amino-5-(4-*t*-butyloxycarbonyl-piperazinyl)- phenyl}benzenesulfonamide and 4-methylsulfonylbenzenesulfonylchloride (61 mg, 0.455 mmol) according to general method 3 to give 70 mg of a purple solid. MS (posES-FIA) m/z = Found: 551.2; Calcd: 551.10.

5 EXAMPLE 24

**2-(Methylsulfonyl)-N-[2-[(phenylsulfonyl)amino]-4-(1-piperazinyl)phenyl]benzenesulfonamide hydrochloride (Scheme 2, Method 4)**

10 2-(Methylsulfonyl)-N-[2-[(phenylsulfonyl)amino]-4-(1-piperazinyl)phenyl]benzenesulfonamide was synthesized from N-{2-amino-5-(4-*t*-butyloxycarbonyl-piperazinyl)- phenyl}benzenesulfonamide and 2-methylsulfonylbenzenesulfonylchloride (61 mg, 0.239 mmol) according to general method 3 to give 70 mg of a purple solid. MS (posES-FIA) m/z = Found: 551.2; Calcd: 551.10; <sup>1</sup>H-NMR δ 8.36-7.46 (m, 9H), 6.95 (d, 1H), 6.68 (dd, 1H), 6.46 (d, 1H), 3.47 (s, 3H), 3.28-3.17 (m, 8H).

15 EXAMPLE 25

20 **2-Methoxy-4-methyl-N-[2-[(phenylsulfonyl)amino]-4-(1-piperazinyl)phenyl]benzenesulfonamide hydrochloride (Scheme 2, Method 4)**

25 2-Methoxy-4-methyl-N-[2-[(phenylsulfonyl)amino]-4-(1-piperazinyl)phenyl]benzenesulfonamide was synthesized from N-{2-amino-5-(4-*t*-butyloxycarbonyl-piperazinyl)- phenyl}benzenesulfonamide and 2-methoxy-4-methylbenzenesulfonylchloride (53 mg, 0.239 mmol) according to general method 3 to give 80 mg of a purple solid. MS (posES-FIA) m/z = Found: 517.2; Calcd 517.15; <sup>1</sup>H NMR δ 7.67-7.37 (m, 6H), 7.10-7.04 (m, 2H), 6.97-6.74 (m, 2H), 6.30 (d, 1H), 4.06 (s, 3H), 3.26-3.09 (m, 8H), 2.37 (s, 3H).

## EXAMPLE 26

**4-Methoxy-2-methyl-N-[2-[(phenylsulfonyl)amino]-4-(1-piperazinyl)phenyl]benzenesulfonamide hydrochloride (Scheme 2, Method 4)**

5        4-Methoxy-2-methyl-N-[2-[(phenylsulfonyl)amino]-4-(1-piperazinyl)phenyl]benzenesulfonamide was synthesized from N-{2-amino-5-(4-*t*-butyloxycarbonyl-piperazinyl)- phenyl}benzenesulfonamide and 2-methyl-4-trifluoromethoxybenzenesulfonylchloride (53 mg, 0.455 mmol) according to general method 3 to give before Boc-deprotection 70 mg of a purple solid. MS (posES-FIA) m/z = Found: 10      571.2; Calcd 571.12; <sup>1</sup>H NMR δ 7.73-7.09 (m, 8H), 6.86 (d, 1H), 6.69 (dd, 1H), 6.48 (d, 1H), 3.29-3.17 (m, 8H), 2.62 (s, 3H).

## EXAMPLE 27

15      **N-{4-(homopiperazinyl)-2-[(phenylsulfonyl)amino]phenyl}benzenesulfonamide hydrochloride (Scheme 1, Method 2)**

Benzenesulfonyl chloride (0.088 g, 0.50 mmol) was added to a solution of 2-amino-5-(4-*t*-butyloxycarbonyl-homopiperazin-1-yl)aniline (0.153 g, 0.50 mmol) and pyridine (514 mL, 6.39 mmol) in DCM. After 1 h at r.t. the mixture was washed with NaHCO<sub>3</sub> (10 %) dried (MgSO<sub>4</sub>) and the solvent was removed. Purification by column chromatography (CH<sub>2</sub>Cl<sub>2</sub>/MeOH/heptane, 4:1:15) gave a mixture of N-{2-amino-4-[4-*t*-butyloxycarbonyl-homopiperazin-1-yl]-phenyl}benzenesulfonamide and of the bis-sulphonylated N-{4-[4-*t*-butyloxycarbonyl] homopiperazinyl)-2-[(phenylsulfonyl)amino]phenyl}benzenesulfonamide (0.150 g, 86 %). Boc-deprotection was achieved by dissolving the mixture in MeOH and adding HCl/ether. The mixture was let at r.t. for 0.5 h. Purification by preparative HPLC gave N-{4-(homopiperazinyl)-2-[(phenylsulfonyl)amino]phenyl}benzenesulfonamide hydrochloride; Anal. (C<sub>23</sub>H<sub>27</sub>ClN<sub>4</sub>O<sub>4</sub>S<sub>2</sub>) C, H, N, S ; M+ 487.4 Calcd 486.14. And N-{4-(homopiperazinyl)-2-[(phenylsulfonyl)amino]phenyl}benzenesulfonamide hydrochloride; Anal. (C<sub>17</sub>H<sub>23</sub>ClN<sub>4</sub>O<sub>2</sub>S) C, H, N, S ; M+ 347.5 Calcd 346.15.

30

## EXAMPLE 28

/O

**N-(4-(1,4-diazepan-1-yl)-2-[(3-fluorophenyl)sulfonyl]amino)phenyl)-3-fluorobenzenesulfonamide hydrochloride (Scheme 1, Method 2)**

The compound was prepared from 2-amino-5-(4-*t*-butyloxycarbonyl-1-homopiperazinyl)aniline and 3-fluorobenzenesulfonyl chloride. Purification by column chromatography (CH<sub>2</sub>Cl<sub>2</sub>/MeOH/heptane, 4:1:15) gave a mixture of N-{2-amino-4-[4-*t*-butyloxycarbonyl-homopiperazin-1-yl]-phenyl} 3-fluorobenzenesulfonamide and N-{4-[4-*t*-butyloxycarbonyl] homopiperazinyl)-2-[(3-fluorophenylsulfonyl)amino]phenyl}-3-fluorobenzenesulfonamide (0.180 g, 73 %). Boc-deprotection was achieved by dissolving the mixture in small amount of MeOH and adding HCl/ether. The mixture was let at r.t. for 0.5 h. Purification by preparative HPLC gave N-(4-(1,4-diazepan-1-yl)-2-[(3-fluorophenyl)sulfonyl]amino)phenyl)-3-fluorobenzenesulfonamide hydrochloride Anal. (C<sub>23</sub>H<sub>27</sub>ClN<sub>4</sub>O<sub>4</sub>S<sub>2</sub>) C, H, N, S; M+ 524.4 Calcd 522.12.

15    **EXAMPLE 29**

**N-{4-(1,4-diazepan-1-yl)-2-[ethyl(phenylsulfonyl)amino]phenyl}benzenesulfonamide hydrochloride (Scheme 1, Method 2)**

A solution of benzenesulfonyl chloride (0.579 mL, 4.53 mmol) in DCM (2.0 mL) was added to tert-butyl 4-[4-amino-3-(ethylamino)phenyl]-1,4-diazepane-1-carboxylate (0.605 g, 1.81 mmol), and pyridine (1.02 mL, 12.67 mmol) in DCM (8.0 mL). The mixture was stirred at room temperature for 16 hours and then concentrated. The crude intermediate was purified by column chromatography on silica using CHCl<sub>3</sub>/10% MeOH + 0.4% NH<sub>3</sub>. Deprotection using HCl-ether/EtOAc gave 0.365 g of the crude product as a HCl-salt. Purification on a reversed phase preparative HPLC gave 94 mg of the product as an acetic acid salt which was converted to the HCl salt and recrystallized from MeOH/Ether: yield 64 mg. <sup>1</sup>H NMR (DMSO-*d*6) δ 9.05 (br s, 2H), 8.66 (s, 1H), 7.89-7.85 (m, 2H), 7.75-7.55 (m, 8H), 7.07 (app d, J=9.1 Hz, 1H), 6.71-6.66 (m, 1H), 5.70 (app d, J=3.2 Hz, 1H), 3.50-3.32 (m, partly obscured by HDO signal, 4H), 3.18-3.14 (m, 2H), 3.05-2.90 (m, 2H), 1.90-1.81 (m, 2H), 0.67 (tr, J=7.2 Hz, 3H); Ms (posES-FIA) *m/z* 515 (M+H)

**Method 4 (Scheme 2)**

Diverse sulfonylchlorides were added to a solution of N-{2-amino-5-(4-*t*-butyloxycarbonyl-1,4-diazepan-1-yl)- phenyl}benzenesulfonamide and pyridine (135  $\mu$ L, 1.7 mmol) in DCM (7mL). After 1 h at r.t. the solvent was removed. Purification by column chromatography (CH<sub>2</sub>Cl<sub>2</sub>/MeOH/Heptane, 4:1:15) followed by Boc-deprotection which was achieved by dissolving the residue in small amount of MeOH and adding HCl/ether. The mixture was left at r.t. for 0.5 h after which the solvent was removed. Recrystallization (MeOH/ether) afforded the final product.

EXAMPLE 30

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**N-{5-(1,4-diazepan-1-yl)-2-[(methylsulfonyl)amino]phenyl}benzenesulfonamide  
(Scheme 2, Method 4)**

N-{5-(1,4-diazepan-1-yl)-2-[(methylsulfonyl)amino]phenyl}benzenesulfonamide was synthesized from N-{2-amino-5-(4-*t*-butyloxycarbonyl-1,4-diazepan-1-yl)- phenyl}benzenesulfonamide (0.075 g, 0.16 mmol) and , methanesulfonyl chloride (0.017 mL, 0.22 mmole) to give 41.6 mg of a light purple solid; Anal. (C<sub>24</sub>H<sub>27</sub>ClN<sub>4</sub>O<sub>3</sub>S x 1.3H<sub>2</sub>O) C, H, N, S.; M<sup>+</sup> 425.4 Calcd 425.12.

EXAMPLE 31

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**N-{5-(1,4-diazepan-1-yl)-2-[(ethylsulfonyl)amino]phenyl}benzenesulfonamide  
hydrochloride (Scheme 2, Method 4)**

N-{5-(1,4-diazepan-1-yl)-2-[(ethylsulfonyl)amino]phenyl}benzenesulfonamide hydrochloride was synthesized from N-{2-amino-5-(4-*t*-butyloxycarbonyl-1,4-diazepan-1-yl)- phenyl}benzenesulfonamide (0.085 g, 0.19 mmol) and ethanesulfonyl chloride (0.032  $\mu$ L, 0.25 mmol) to give 29.1 mg of a light purple solid; Anal. (C<sub>24</sub>H<sub>27</sub>ClN<sub>4</sub>O<sub>3</sub>S x 0.75H<sub>2</sub>O) C, H, N, S.; M<sup>+</sup> 439.4 Calcd 439.14.

EXAMPLE 32

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**N-{4-(1,4-diazepan-1-yl)-2-[(phenylsulfonyl)amino]phenyl}[1,1'-biphenyl]-4-sulfonamide hydrochloride (Scheme 2, Method 4)**

N-{4-(1,4-diazepan-1-yl)-2-[(phenylsulfonyl)amino]phenyl}[1,1'-biphenyl]-4-sulfonamide hydrochloride was synthesized from N-{2-amino-5-(4-*t*-butyloxycarbonyl-1,4-diazepan-1-yl)- phenyl}benzenesulfonamide (0.081 g, 0.18 mmol) and , 1,1'-biphenyl-4-sulfonyl chloride (0.059 g, 0.24 mmol) to give 42.9 mg of a light purple solid; Anal. (C<sub>24</sub>H<sub>27</sub>ClN<sub>4</sub>O<sub>3</sub>S) C, H, N, S.; M+ 563.5 Calcd 563.17.

**EXAMPLE 33**

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**N-(2,1,3-benzoxadiazol-4-yl)-4-(1,4-diazepan-1-yl)-2-[(phenylsulfonyl)amino]benzenesulfonamide hydrochloride (Scheme 2, Method 4)**

N-(2,1,3-benzoxadiazol-4-yl)-4-(1,4-diazepan-1-yl)-2-[(phenylsulfonyl)amino]benzenesulfonamide hydrochloride was synthesized from N-{2-amino-5-(4-*t*-butyloxycarbonyl-1,4-diazepan-1-yl)- phenyl}benzenesulfonamide (0.072 g, 0.16 mmol) and 2,1,3-benzoxadiazol-4-yl sulfonyl chloride (0.072 g, 0.21 mmol) to give 38.0 mg of a light purple solid; M+1 537.2 Calcd 537.15; <sup>1</sup>HNMR δ 8.21 (d, 1H), 7.80 (d, 1H), 7.68-7.46 (m, 6H), 6.92 (d, 1H), 6.49 (dd, 1H), 6.12 (d, 1H), 3.57 (app t, 2H), 3.34 (app t, 2H), 3.17 (app t, 2H), 3.11 (app t, 2H), 2.03-1.95 (m, 2H).

20

**EXAMPLE 34**

**N-{4-(1,4-diazepan-1-yl)-2-[(phenylsulfonyl)amino]phenyl}-2-naphthalenesulfonamide hydrochloride (Scheme 2, Method 4)**

N-{4-(1,4-diazepan-1-yl)-2-[(phenylsulfonyl)amino]phenyl}-2-naphthalenesulfonamide hydrochloride was synthesized from N-{2-amino-5-(4-*t*-butyloxycarbonyl-1,4-diazepan-1-yl)- phenyl}benzenesulfonamide (0.084 g, 0.19 mmol) and , 2-naphtylsulfonyl chloride (0.055 mL, 0.24 mmol) to give 67.8 mg of a light purple solid; Anal. (C<sub>24</sub>H<sub>27</sub>ClN<sub>4</sub>O<sub>3</sub>S) C, H, N, S; M+ 529.2 Calcd 529.12.

30

**EXAMPLE 35**

**N-{4-(1,4-diazepan-1-yl)-2-[(methylsulfonyl)amino]phenyl}benzenesulfonamide hydrochloride (Scheme 2, Method 4)**

Benzenesulfonylchloride (0.233 g, 1.8 mmol) was added to a solution of N-{5-(4-t-butyloxycarbonyl-1,4-diazepan-1-yl)-2-amino]phenyl}methanesulfonamide (0.540 g, 1.4 mmol) and pyridine (0.995 mL, 12.6 mmol) in DCM (40 mL). After 2 h at rt the solvent was removed. Purification by column chromatography (DCM/MeOH/heptane 4:1:5) gave 580 mg (79 %) of a light purple solid. Boc-deprotection was carried out by dissolving the compound in small amount of MeOH and adding HCl/ether. The solvent was removed and the product was recrystallized from MeOH/ether. M+1 425.2 Calcd 425.12

**EXAMPLE 36**

**N-{4-(1,4-diazepan-1-yl)-2-[methyl(methylsulfonyl)amino]phenyl}benzenesulfonamide hydrochloride (Scheme 2, Method 4)**

MeI (45  $\mu$ L, 0.72 mmol) was added to a mixture of N-{4-(4-t-butyloxycarbonyl-1,4-diazepan-1-yl)-2-[(methylsulfonyl)amino]phenyl}benzenesulfonamide (0.189 g, 0.36 mmol) and K<sub>2</sub>CO<sub>3</sub> (0.124, 0.90 mmol) in acetone (25 mL). The mixture was stirred at r.t. for 2 h, filtered and the solvent was removed. Column chromatography (DCM/MeOH/Heptane 4:1:15) gave 110 mg of N-{4-(4-t-butyloxycarbonyl-1,4-diazepan-1-yl)-2-[methyl(methylsulfonyl)amino]-phenyl}benzenesulfonamide and 20 mg of N-{4-(4-t-butyloxycarbonyl-1,4-diazepan-1-yl)-2-[(methylsulfonyl)amino]phenyl}-N-methylbenzenesulfonamide. Boc-deprotection was carried out by dissolving the compounds in small amount of MeOH and adding HCl/ether. The solvent was removed and the products were recrystallized from MeOH/ether. N-{4-(1,4-diazepan-1-yl)-2-[methyl(methylsulfonyl)amino]phenyl}benzenesulfonamide hydrochloride M+1 439.2 Calcd 439.14.

**EXAMPLE 37**

**N-{4-(1,4-diazepan-1-yl)-2-[(methylsulfonyl)amino]phenyl}-N-methylbenzenesulfonamide hydrochloride (Scheme 2, Method 4)**

MeI (45  $\mu$ L, 0.72 mmol) was added to a mixture of N-{4-(4-t-butyloxycarbonyl-1,4-diazepan-1-yl)-2-[(methylsulfonyl)amino]phenyl}benzenesulfonamide (0.189 g, 0.36 mmol) and K<sub>2</sub>CO<sub>3</sub> (0.124, 0.90 mmol) in acetone (25 mL). The mixture was stirred at r.t. for 2 h, filtered and the solvent was removed. Purification by column chromatography (DCM/MeOH/Heptane 4:1:15) gave 110 mg of N-{4-(4-t-butyloxycarbonyl-1,4-diazepan-1-yl)-2-[(methylsulfonyl)amino]phenyl}benzenesulfonamide and 20 mg of N-{4-(4-t-butyloxycarbonyl-1,4-diazepan-1-yl)-2-[(methylsulfonyl)amino]phenyl}-N-methylbenzenesulfonamide. Boc-deprotection was carried out by dissolving the compounds in small amount of MeOH and adding HCl/ether. The solvent was removed and the products were recrystallized from MeOH/ether. N-{4-(1,4-diazepan-1-yl)-2-[(methylsulfonyl)amino]phenyl}-N-methylbenzenesulfonamide hydrochloride M+1 439.2 Calcd 439.14.

15    **EXAMPLE 38**

**N-{4-(1,4-diazepan-1-yl)-2-[methyl(phenylsulfonyl)amino]phenyl}benzenesulfonamide hydrochloride (Scheme 2, Method 4)**

MeI (45  $\mu$ L, 0.72 mmol) was added to a mixture of N-{4-(4-t-butyloxycarbonyl-1,4-diazepan-1-yl)-2-[(phenylsulfonyl)amino]phenyl}benzenesulfonamide (0.189 g, 0.36 mmol) and K<sub>2</sub>CO<sub>3</sub> (0.124, 0.90 mmol) in acetone (25 mL). The mixture was stirred at r.t. for 2 h, filtered and the solvent was removed. Purification by column chromatography (DCM/MeOH/heptane 4:1:15) gave N-{4-(4-t-butyloxycarbonyl-1,4-diazepan-1-yl)-2-[methyl(phenylsulfonyl)-amino]phenyl}benzenesulfonamide as a colourless oil. Boc-deprotection was carried out by dissolving the compound in small amount of MeOH and adding HCl/ether. The solvent was removed and the residue was recrystallized from MeOH/ether to give 62.7 mg of product M+1 501.3 Calcd 501.16.

**Scheme 3**

30    To a solution of N-{2-amino-5-(4-t-butyloxycarbonyl-1,4-diazepan-1-yl)- phenyl}

VO

methanesulfonamide (134 mg, 0.35 mmol) and pyridine (250 µL, 3.14 mmole) in DCM (7mL), the sulfonylchloride (0.455 mmol) was added. After 2 h at r.t. the solvent was removed. Purification by column chromatography (CH<sub>2</sub>Cl<sub>2</sub>/MeOH/Heptane, 4:1:15) followed by Boc-deprotection which was achieved by dissolving the residue in small amount of MeOH and adding HCl/ether. The mixture was left at r.t. for 0.5 h after which the solvent was removed. Recrystallization (MeOH/ether) afforded the final product.

#### EXAMPLE 39

10 **N-{4-(1,4-diazepan-1-yl)-2-[(methylsulfonyl)amino]phenyl}-1-naphthalenesulfonamide hydrochloride (Scheme 3)**

The compound was synthesized from N-{2-amino-5-(4-*t*-butyloxycarbonyl-1,4-diazepan-1-yl)- phenyl}methanesulfonamide and 1-naphthalenesufonylchloride (103 mg, 0.455 mmol) to give before Boc-deprotection 150 mg of a purple solid. M+1 475.1 Calcd 474.14.

#### EXAMPLE 40

20 **N-{4-(1,4-diazepan-1-yl)-2-[(methylsulfonyl)amino]phenyl}-2-naphthalenesulfonamide hydrochloride (Scheme 3)**

The compound was synthesized from N-{2-amino-5-(4-*t*-butyloxycarbonyl-1,4-diazepan-1-yl)- phenyl}methanesulfonamide and 2-naphthalenesufonylchloride (103 mg, 0.455 mmol) to give before Boc-deprotection 120 mg of a purple solid. M+1 475.1 Calcd 474.14.

25

#### EXAMPLE 41

30 **N-{4-(1,4-diazepan-1-yl)-2-[(methylsulfonyl)amino]phenyl}-4-fluorobenzenesulfonamide hydrochloride (Scheme 3)**

The compound was synthesized from N-{2-amino-5-(4-*t*-butyloxycarbonyl-1,4-diazepan-1-yl)- phenyl}methanesulfonamide and 4-fluorobenzenesulfonylchloride (89 mg,

0.455 mmol) to give before Boc-deprotection 170 mg of a purple solid. M+1 443.1 Calcd 443.11.

#### EXAMPLE 42

5

**N-{4-(1,4-diazepan-1-yl)-2-[(methylsulfonyl)amino]phenyl}-4-nitrobenzenesulfonamide hydrochloride (Scheme 3)**

The compound was synthesized from N-{2-amino-5-(4-*t*-butyloxycarbonyl-1,4-diazepan-1-yl)- phenyl}methanesulfonamide and 4-nitrobenzenesulfonylchloride (101 mg, 0.455 mmol) according to general method 3 to give before Boc-deprotection 118 mg of a purple solid. M+1 470.1 Calcd 470.11.

#### EXAMPLE 43

15    **N-{4-(1,4-diazepan-1-yl)-2-[(methylsulfonyl)amino]phenyl}-3-(trifluoromethyl)- benzenesulfonamide hydrochloride (Scheme 3)**

The compound was synthesized from N-{2-amino-5-(4-*t*-butyloxycarbonyl-1,4-diazepan-1-yl)- phenyl}methanesulfonamide and 3-trifluoromethylbenzenesulfonylchloride (111 mg, 0.455 mmol) to give before Boc-deprotection 145 mg of a purple solid. M+1 493.1 Calcd 493.11.

#### EXAMPLE 44

25    **N-{4-(1,4-diazepan-1-yl)-2-[(methylsulfonyl)amino]phenyl}-2-methylbenzenesulfonamide hydrochloride (Scheme 3)**

The compound was synthesized from N-{2-amino-5-(4-*t*-butyloxycarbonyl-1,4-diazepan-1-yl)- phenyl}methanesulfonamide and o-toluenesulfonylchloride (87 mg, 0.455 mmol) to give before Boc-deprotection 175 mg of a purple solid. M+1 439.2 Calcd 438.14.

30    EXAMPLE 45

**N-{4-(1,4-diazepan-1-yl)-2-[(methylsulfonyl)amino]phenyl}-4-(trifluoromethoxy)-benzenesulfonamide hydrochloride (Scheme 3)**

The compound was synthesized from N-{2-amino-5-(4-*t*-butyloxycarbonyl-1,4-diazepan-1-yl)- phenyl} methanesulfonamide and 4-trifluoromethoxybenzenesulfonylchloride (119 mg, 0.455 mmol) give 140 mg as a purple solid. M+1 509.1 Calcd 509.11.

**EXAMPLE 46**

**N-{4-(1,4-diazepan-1-yl)-2-[(methylsulfonyl)amino]phenyl}-3,5-dimethyl-4-**

**isoxazolesulfonamide hydrochloride (Scheme 3)**

The compound was synthesized from N-{2-amino-5-(4-*t*-butyloxycarbonyl-1,4-diazepan-1-yl)- phenyl} methanesulfonamide and 3,5-dimethylisoxazole-4-sulfonylchloride (89 mg, 0.455 mmol) 3 to give 120 mg of as purple solid. M+1 444.2 Calcd 444.13.

**EXAMPLE 47**

**N-{4-(1,4-diazepan-1-yl)-2-[(methylsulfonyl)amino]phenyl}-3-methoxybenzene-sulfonamide hydrochloride (Scheme 3)**

The compound was synthesized from N-{2-amino-5-(4-*t*-butyloxycarbonyl-1,4-diazepan-1-yl)- phenyl} methanesulfonamide and 3-methoxybenzenesulfonylchloride (94 mg, 0.455 mmol) to give 160 mg as a purple solid. M+1 455.2 Calcd 455.13.

**INTERMEDIATE 11**

**tert-Butyl 4-{4-[(4-methylphenyl)sulfonyl]amino}-3-[(methylsulfonyl)amino]phenyl}-1,4-diazepane-1-carboxylate (scheme 2, Method 4)**

*tert*-Butyl 4-{4-nitro-3-[(methylsulfonyl)amino]phenyl}-1,4-diazepane-1-carboxylate (1 g, 2.4 mmol) was dissolved in THF (20 mL) and methanol (2 mL). Raney nickel (0.2 g) was added followed by hydrazine hydrate (0.2 mL). Nitrogen was evolved and the mixture stirred for 1 hour. The reaction was shown to be incomplete by tlc (CH<sub>2</sub>Cl<sub>2</sub>, MeOH 9:1) so a further 0.1mL of hydrazine hydrate was added. After a further hour, the reaction mixture

was absorbed onto a bed of silica gel and eluted with CH<sub>2</sub>Cl<sub>2</sub>:MeOH:NH<sub>4</sub>OH (9:1:0.01 150 mL). The solvent was removed by evaporation, toluene (100 mL) was added and evaporated to remove any water and hydrazine. The crude amine (0.9 g) was dissolved in acetonitrile (20 mL). To this solution under nitrogen was added dimethylaminopyridine (0.32 g) and 5 toluenesulfonyl chloride (0.51 g) and the mixture stirred for 3 hours. The solution was poured into water (100 mL) and extracted with ethyl acetate (30 mL). The organic extract was washed with water, dried over MgSO<sub>4</sub> and evaporated to give 0.83 g of crude product which was purified by flash chromatography (EtOAc:Petrol 1:1). Yield 0.53 g (41%) <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.38, 1.40 (2s, 9 H), 1.91 (m, J = 6.11 Hz, 2 H), 2.44 (s, 3 H), 3.03, 3.05 (2s, 10 3 H), 3.16-3.33 (m, 2 H), 3.46-3.57 (m, 6 H), 6.02 (s, 1 H), 6.21 (ab, J = 9.03 Hz, 1 H), 6.30 (ab, J = 9.03 Hz, 1 H), 6.97 (d, J = 2.69 Hz, 1 H), 7.27 (ab, J = 8.55 Hz, 2 H), 7.33, 7.36 (2s, 1 H), 7.57 (ab, J = 8.06 Hz, 2 H); MS (ESI+) for C<sub>24</sub>H<sub>34</sub>N<sub>4</sub>O<sub>6</sub>S<sub>2</sub> m/z 561.1800 (M+)<sup>+</sup> (Calculated 561.1817).

## 15 EXAMPLE 48

**N-{4-(1,4-diazepan-1-yl)-2-[(methylsulfonyl)amino]phenyl}-4-methylbenzenesulfonamide hydrochloride (PHA 516123A)**

tert-Butyl 4-{4-{{[(4-methylphenyl)sulfonyl]amino}-3-[(methylsulfonyl)amino]phenyl}-1,4-diazepane-1-carboxylate (0.5 g) was dissolved in methanol (15 mL). A solution of HCl in ethyl acetate (1N, 25 mL) was added and the mixture stirred for 2 hours. Ether (200 mL) was added and the mixture stirred for 3 hours to allow full precipitation. The product was collected by filtration, washed with ether and dried. Yield 0.43 g (98%) <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ 2.03 (m, 2 H), 2.36 (s, 3 H), 2.9 (s, 3 H), 3.02-3.09 (br m, 2 H), 3.11-3.19 (br m, 2 H), 3.41 (br t, J = 7.08 Hz, 2 H), 3.63 (br m, 2 H), 6.46 (d ab, J = 2.8 Hz, 8.8Hz, 1 H), 6.62 (ab, J = 8.8 Hz, 1 H), 6.71 (d, J = 2.8 Hz, 1 H), 7.36 (ab, J = 8.3 Hz, 2 H), 7.58 (ab, J = 8.3 Hz, 2 H), 8.39 (s, 1 H), 9.2 (br, 2 H), 9.8 (s, 1 H); MS (ESI+) for C<sub>19</sub>H<sub>27</sub>N<sub>4</sub>O<sub>4</sub>S<sub>2</sub> m/z 439.148 (M+H)<sup>+</sup> (Calculated 439.1474).

## 30 INTERMEDIATE 12

**N-ethyl-N-(5-fluoro-2-nitrophenyl)methanesulfonamide (Scheme 2, Method 4)**

N-ethyl-methanesulfonamide (Mijs *et al.* J.Chem.Soc.Chem.Com. 1972 p412) (5 g 40.6 mmol) was added to a suspension of sodium hydride (1.9 g, 55% in mineral oil) in anhydrous DMF (100 mL) under nitrogen. The mixture was warmed to 55°C for one hour 5 and 2,4-difluoronitrobenzene (4.4 mL) was added dropwise. The reaction was stirred at 60°C overnight, poured into water (500 mL) and the product extracted into CH<sub>2</sub>Cl<sub>2</sub> (5 x 100mL). The organic extracts were washed with water, dried over MgSO<sub>4</sub> and evaporated to give an oily product. The remaining DMF was removed by trituration with petrol. The crude 10 product was purified by flash chromatography (ethyl acetate:petrol 1:1) to yield the desired product which was recrystallised from ethanol. Yield 3.5g (33%). Calculated N % 10,68 C % 41,22 S % 12,23 H % 4,23; Found N % 10,68 C % 41,39 S % 12,22 H % 4,17.

## INTERMEDIATE 13

**15 tert-Butyl 4-[3-[ethyl(methylsulfonyl)amino]-4-nitrophenyl]-1,4-diazepane-1-carboxylate (Scheme 2, Method 4)**

N-Ethyl-N-(5-fluoro-2-nitrophenyl)methanesulfonamide (3.2 g, 12.2 mmol), *tert*-butyl 1-homopiperazinecarboxylate (2.5 g) and potassium carbonate (2 g) were heated together in DMSO at 50 °C for 5 hours. The solution was allowed to cool and poured into 20 500 mL of water. The solid product was collected by filtration, washed with water and dried. The product was purified by flash chromatography (ethyl acetate:petrol 1:1). Yield 2.6g (48%) <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.16 (t, *J* = 7.33 Hz, 3 H), 1.39 (s, 9 H), 2.0 (br, 2 H), 2.99 (s, 3 H), 3.2 (br, 2 H), 3.54-3.75 (br, 8 H), 6.65 (br d, *J* = 9.3 Hz, 1 H), 6.67 (d, *J* = 2.93 Hz, 1 H), 8.1 (d, *J* = 9.3 Hz, 1 H); MS (ESI+) for C<sub>19</sub>H<sub>30</sub>N<sub>4</sub>O<sub>6</sub>S *m/z* 442 (M<sup>+</sup>).

25

*Preparation of N-[4-(1,4-diazepan-1-yl)-2-[ethyl(methylsulfonyl)amino]phenyl]-sulfonamides*

tert-Butyl 4-[3-[ethyl(methylsulfonyl)amino]-4-nitrophenyl]-1,4-diazepane-1-carboxylate (2.5 g, 5.7 mmol) was dissolved in THF (50 mL) and methanol (5 mL). Raney 30 nickel (0.5 g) was added followed by hydrazine hydrate (0.5 mL). Nitrogen was evolved and the mixture stirred for 1 hour. The reaction mixture was absorbed onto a bed of silica gel and

eluted with CH<sub>2</sub>Cl<sub>2</sub>:MeOH:NH<sub>4</sub>OH (9:1:0.01 200 mL). The solvent was removed by evaporation, toluene (200 mL) was added and evaporated to remove any water and hydrazine. The crude amine (2.15 g) was dissolved in acetonitrile (50 mL) with dimethylaminopyridine (0.8 g). This solution was divided into three portions. To each 5 portion was added a sulfonyl chloride (2.2 mmol) and the mixtures were stirred overnight at 40°C. The reactions were worked up by adding to water (150 mL), extracting the product into ethyl acetate, washing with water, drying over MgSO<sub>4</sub> and evaporating. Each of the crude boc protected products was purified by flash chromatography (ethyl 10 acetate:petrol 1:1). They were then deprotected directly by dissolving in methanol (10 mL), adding a solution of HCl in ethyl acetate (1N, 50 mL) and stirring for 2 hours. The products were precipitated with ether (500 mL), collected by filtration and dried under vacuum. The products obtained were:

#### EXAMPLE 49

15

**N-{4-(1,4-diazepan-1-yl)-2-[ethyl(methylsulfonyl)-amino]phenyl}-4-methylbenzenesulfonamide hydrochloride (Scheme 2, Method 4)**

Was obtained from toluene sulfonyl chloride: Yield 0.36 g

18 <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 0.79 (t, *J* = 7.08 Hz, 3 H), 2.04 (m, 2 H), 2.37 (s, 3 H), 20 3.07 (s, 3 H), 3.02-3.12 (br, 2 H), 3.12-3.20 (br, 2 H), 3.45 (t, *J* = 5.85 Hz, 2 H), 3.50 (q, *J* = 7.08 Hz, 2 H), 3.67 (br, 2 H), 6.65-6.73 (m, 2 H), 6.94 (d, *J* = 9.03 Hz, 1 H), 7.38 (ab, *J* = 8.06 Hz, 2 H), 7.70 (ab, *J* = 8.06 Hz, 2 H), 8.52 (s, 1 H), 9.2 (br s, 2 H)  
MS (ESI+) for C<sub>21</sub>H<sub>30</sub>N<sub>4</sub>O<sub>4</sub>S<sub>2</sub> *m/z* 466.1722 M<sup>+</sup> (Calc 466.1708).

25 EXAMPLE 50

**N-{4-(1,4-diazepan-1-yl)-2-[ethyl-(methylsulfonyl)-amino]phenyl}-3,4-dimethoxybenzenesulfonamide hydrochloride (Scheme 2, Method 4)**

Was obtained from 3,4-dimethoxybenzenesulfonyl chloride: Yield 0.43 g

30 <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 0.81 (t, *J* = 7.08 Hz, 3 H), 2.05 (m, 2 H), 3.08 (s, 3 H), 3.03-3.11 (br, 2 H), 3.11-3.19 (br, 2 H), 3.45 (t, *J* = 6.10 Hz, 2 H), 3.52 (q, *J* = 7.08 Hz, 2 H),

3.68 (br t,  $J = 5.13$  Hz, 2 H), 3.77 (s, 3 H), 3.81 (s, 3 H), 6.66-6.74 (m, 2 H), 6.97 (d,  $J = 8.79$  Hz, 1 H), 7.09 (d,  $J = 8.55$  Hz, 1 H), 7.33-7.4 (m, 2 H), 8.49 (s, 1 H), 9.3 (br s, 2 H)  
MS (ESI+) for  $C_{22}H_{32}N_4O_6S_2$   $m/z$  512.1759 M<sup>+</sup> (Calc 512.1763).

5 EXAMPLE 51

**N-{4-(1,4-diazepan-1-yl)-2-[ethyl(methylsulfonyl)amino]phenyl}-8-quinolinesulfonamide hydrochloride (Scheme 2, Method 4)**

Was obtained from 8-quinoline sulfonyl chloride: Yield 0.46 g

10  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  0.17 (t,  $J = 7.08$  Hz, 3 H), 2.06 (m, 2 H), 2.93 (s, 3 H), 3.0-3.2 (m, 6 H), 3.47 (t,  $J = 5.86$  Hz, 2 H), 3.70 (t,  $J = 5.12$  Hz, 2 H), 6.59 (m, 1 H), 6.77 (d m,  $J = 9$  Hz, 1 H), 7.31 (d,  $J = 9$  Hz, 1 H), 7.65-7.75 (m, 2 H), 8.24 (d,  $J = 7.32$  Hz, 1 H), 8.29 (d,  $J = 9.5$  Hz, 1 H), 8.55 (dd,  $J = 8.55, 1.71$  Hz, 1 H), 9 (br, 1 H), 9.09 (dd,  $J = 4.16, 1.71$  Hz, 1 H), 9.3 (br, 2 H); MS (ESI+) for  $C_{23}H_{29}N_5O_4S_2$   $m/z$  503.1667 M<sup>+</sup> (Calc 503.1661).

15

**INTERMEDIATE 14**

**N-(5-fluoro-2-nitrophenyl)methanesulfonamide (Scheme 2, Method 4)**

2,4-di-Nitrobenzene (5.5mL, 50mmol), methanesulfonamide (4.75g, 50mmol) and 20 potassium carbonate (10g) were stirred together in DMSO (100mL) at 80°C overnight. Water (300mL) was added followed by hydrochloric acid (1N, 300mL). The solid product was collected by filtration, washed with water and dried. Yield 9.57g (82%)

$^1H$  NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  3.2 (s, 3 H), 6.92 (m, 1 H), 7.64 (dd,  $J = 10.5, 2.7$  Hz, 1 H), 8.34 (dd,  $J = 9.5, 5.6$  Hz, 1 H), 10.0 (brs, 1 H); MS (ESI+) for  $C_7H_7FN_2O_4S$   $m/z$  234 M<sup>+</sup>.

25

**INTERMEDIATE 15**

**N-(5-Fluoro-2-nitrophenyl)-N-methylmethanesulfonamide (Scheme 2, Method 4)**

30 N-(5-fluoro-2-nitrophenyl)methanesulfonamide compound (5g, 21mmol), methyl iodide (3mL) and potassium carbonate (10g) were stirred together in DMSO (100mL) at 80°C overnight. The reaction was not complete and a further 1mL of methyl iodide was

added. After a further 24 hours at 80°C, water (1000mL) was added. The solution was decanted from a small amount of sticky residue. The product crystallized out from the aqueous solution (48 hours) and was collected by filtration, washed with water and dried.

Yield 3.3g (63%);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  3.04 (s, 3 H), 3.30 (s, 3 H), 7.20 (m, 1 H),  
5 7.31 (dd,  $J = 8.54, 2.68$  Hz, 1 H), 8.0 (dd,  $J = 9.3, 5.6$  Hz, 1 H); MS (ESI+) for  $\text{C}_8\text{H}_9\text{FN}_2\text{O}_4\text{S}$   $m/z$  248  $\text{M}^+$ .

## INTERMEDIATE 16

10 **tert-Butyl-4-{3-[methyl(methylsulfonyl)amino]-4-nitrophenyl}-1,4-diazepane-1-carboxylate (Scheme 2, Method 4)**

N-(5-Fluoro-2-nitrophenyl)-N-methylmethanesulfonamide (3.1 g, 12.5 mmol), *tert*-butyl 1-homopiperazinecarboxylate (2.5 g) and potassium carbonate (2 g) were heated together in DMSO (50 mL) at 80 °C overnight. The solution was allowed to cool and poured into 500 mL of water. The solid product was collected by filtration, washed with water and dried. Yield 4.6 g (86%);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.41 (s, 9 H), 2.0 (br s, 2 H), 3.01 (s, 3 H), 3.28 (s, 3 H), 3.3-3.8 (br, 8 H), 6.64 (d,  $J = 8.1$  Hz, 1 H), 6.74 (d,  $J = 4.8$  Hz, 1 H), 8.09 (d,  $J = 8.1$  Hz, 1 H); MS (ESI+) for  $\text{C}_{18}\text{H}_{28}\text{N}_4\text{O}_6\text{S}$   $m/z$  428.1709 ( $\text{M}^+$ ) (calc. 428.1730).

20 *Preparation of N-{4-(1,4-diazepan-1-yl)-2-[methyl(methylsulfonyl)amino]phenyl}-sulfonamides*

tert-Butyl-4-{3-[methyl(methylsulfonyl)amino]-4-nitrophenyl}-1,4-diazepane-1-carboxylate (2.5 g, 5.7 mmol) was dissolved in THF (50 mL) and methanol (5 mL). Raney nickel (0.5 g) was added followed by hydrazine hydrate (0.5 mL). Nitrogen was evolved and the mixture stirred for 1 hour. The reaction mixture was absorbed onto a bed of silica gel and eluted with  $\text{CH}_2\text{Cl}_2:\text{MeOH}:\text{NH}_4\text{OH}$  (9:1:0.01 200 mL). The solvent was removed by evaporation, toluene (200 mL) was added and evaporated to remove any water and hydrazine. The crude amine (2.36 g) was dissolved in acetonitrile (50 mL) with dimethylaminopyridine (0.8 g). This solution was divided into six portions. To three of these portions was added a sulfonyl chloride (1.1 mmol) and the mixtures were stirred overnight at 40°C. The reactions were worked up by adding ethyl acetate (50 mL), washing

with brine and water, drying over MgSO<sub>4</sub> and evaporating. Each of the crude boc protected products was purified by flash chromatography (ethyl acetate:petrol 2:1). They were then deprotected directly by dissolving in methanol (10 mL), adding a solution of HCl in ethyl acetate (1N, 50 mL) and stirring for 2 hours. The products were precipitated with ether (500 mL), collected by filtration and dried under vacuum.

The products obtained were:

EXAMPLE 52

10 N-{4-(1,4-diazepan-1-yl)-2-[methyl(methylsulfonyl)-amino]phenyl}-4-methylbenzenesulfonamide hydrochloride (Scheme 2, Method 4)

Was obtained from toluene sulfonyl chloride: Yield 0.18g

<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 2.04 (br m, 2 H), 2.36 (s, 3 H), 2.72 (s, 3 H), 3.05 (s, 3 H), 3.1-3.4 (m, 4 H), 3.46 (t, *J* = 6.34 Hz, 2 H), 3.70 (t, *J* = 4.88 Hz, 2 H), 6.69 (d, *J* = 2.7 Hz, 1 H), 6.72 (s, 1 H), 6.95 (d, *J* = 8.78 Hz, 1 H), 7.36 (ab, *J* = 8.54 Hz, 2 H), 7.57 (ab, *J* = 8.54 Hz, 2 H), 8.39 (s, 1 H), 9.24 (brs, 2 H); MS (ESI+) for C<sub>20</sub>H<sub>23</sub>N<sub>4</sub>O<sub>4</sub>S<sub>2</sub> *m/z* 452.1545 M<sup>+</sup> (Calc. 452.1552).

EXAMPLE 53

20

N-{4-(1,4-diazepan-1-yl)-2-[methyl-(methyl-sulfonyl)amino]phenyl}-naphthalene-2-sulfonamide hydrochloride (Scheme 2, Method 4)

Was obtained from 2-naphthalenesulfonyl chloride: Yield 0.09g

<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 2.0 (br m, 2 H), 2.66 (s, 3 H), 3.05 (s, 3 H), 3.0-3.4 (m, 4 H), 3.43 (t, *J* = 7.08 Hz, 2 H), 3.66 (br t, *J* = 5.1 Hz, 2 H), 6.65 (dd, *J* = 9.0, 2.9 Hz, 1 H), 6.68 (s, 1 H), 6.90 (d, *J* = 9.0 Hz, 1 H), 7.65 (q, *J* = 8.0 Hz, 1 H), 7.68 (q, *J* = 8.3 Hz, 1 H), 7.8 (d, *J* = 6.8 Hz, 1 H), 8.04 (d, *J* = 7.8 Hz, 1 H), 8.12 (t, *J* = 8.8 Hz, 2 H), 8.32 (s, 1 H), 8.68 (s, 1 H), 9.2 (br, 2 H); MS (ESI+) for C<sub>23</sub>H<sub>28</sub>N<sub>4</sub>O<sub>4</sub>S<sub>2</sub> *m/z* 488.1529 M<sup>+</sup> (Calc. 488.1552).

30 EXAMPLE 54

**N-{4-(1,4-diazepan-1-yl)-2-[methyl(methylsulfonyl)amino]phenyl}-5-(2-pyridinyl)-2-thiophenesulfonamide hydrochloride (Scheme 2, Method 4)**

Was obtained from 5-(2-pyridinyl)thiophene-2-sulfonyl chloride: Yield 0.12 g

<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 2.05 (br m, 2 H), 2.90 (s, 3 H), 3.07 (s, 3 H), 3.1-3.4 (m, 4 H), 3.48 (t, *J* = 6.1 Hz, 2 H), 3.71 (m, 2 H), 6.75 (dd, *J* = 9.0, 2.7 Hz, 1 H), 6.78 (s, 1 H), 7.03 (d, *J* = 8.8 Hz, 1 H), 7.39 (dd, *J* = 7.6, 4.2 Hz, 1 H), 7.50 (d, *J* = 4.2 Hz, 1 H), 7.84 (d, *J* = 3.9 Hz, 1 H), 7.91 (td, *J* = 7.6, 1.7 Hz, 1 H), 8.03 (d, *J* = 7.8 Hz, 1 H), 8.56 (d, *J* = 4.9 Hz, 1 H), 8.81 (s, 1 H), 9.3 (br, 2 H); MS (ESI+) for C<sub>22</sub>H<sub>27</sub>N<sub>5</sub>O<sub>4</sub>S<sub>3</sub> *m/z* 521.1200 M<sup>+</sup> (Calc. 521.1225).

10 **Scheme 3**

To a solution of N-{2-amino-5-(4-*t*-butyloxycarbonyl-1,4-diazepan-1-yl)- phenyl} benzenesulfonamide (92.5 mg, 0.207 mmol) and pyridine (131 μL, 1.6 mmol) in DCM (7 mL), the sulfonylchloride (0.27 mmol) was added. After 2 h at r.t. the solvent was removed. 15 Purification by columnchromatography (CH<sub>2</sub>Cl<sub>2</sub>/MeOH/Heptane, 4:1:15) followed by Boc-deprotection which was achieved by dissolving the residue in small amount of MeOH and adding HCl/ether. The mixture was left at r.t. for 0.5 h after which the solvent was removed. Recrystallization (MeOH/ether) afforded the final product.

20 **EXAMPLE 55**

25 **N-{4-(1,4-diazepan-1-yl)-2-[(phenylsulfonyl)amino]phenyl}-1-naphthalenesulfonamide hydrochloride (Scheme 3)**

The compound was synthesized from of N-{2-amino-5-(4-*t*-butyloxycarbonyl-1,4-diazepan-1-yl)- phenyl}benzenesulfonamide and 1-naphthalenesulfonylchloride (61 mg, 0.27 mmol) to give 56 mg as purple solid. M+1 537.2 Calcd 537.15; <sup>1</sup>HNMR δ 8.67-8.64 (m, 1H), 8.10 (d, 1H), 8.02-7.98 (m, 1H), 7.89 (dd, 1H), 7.77-7.38 (m, 8H), 6.46 (d, 1H), 6.26 (d, 1H), 30 6.14 (dd, 1H), 3.54 (app t, 2H), 3.36-3.31 (m, 2H), 3.17 (app t, 2H), 2.05-1.96 (m, 2H).

**EXAMPLE 56**

**N-{4-(1,4-diazepan-1-yl)-2-[(phenylsulfonyl)amino]phenyl}-5-(dimethylamino)-1-naphthalenesulfonamide hydrochloride (Scheme 3)**

The compound was synthesized from of N-{2-amino-5-(4-*t*-butyloxycarbonyl-1,4-diazepan-1-yl)- phenyl}benzenesulfonamide and dansylchloride (73 mg, 0.27 mmol) to give  
5 51 mg AS purple solid. M+1 580.3 Calcd 580.20;  $^1\text{H}$ NMR  $\delta$  8.86 (d, 1H), 8.62 (d, 1H), 8.08-7.46 (m, 9H), 6.64 (d, 1H), 6.32 (dd, 1H), 6.14 (d, 1H), 3.53 (app t, 2H), 3.45 (s, 6H), 3.16-3.06 (m, 4H), 2.03-1.95 (m, 2H).

**EXAMPLE 57**

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**N-{4-(1,4-diazepan-1-yl)-2-[(phenylsulfonyl)amino]phenyl}-8-quinolinesulfonamide hydrochloride (Scheme 3)**

The compound was synthesized from of N-{2-amino-5-(4-*t*-butyloxycarbonyl-1,4-diazepan-1-yl)- phenyl}benzenesulfonamide and 8-quinolinesulfonylchloride (61 mg, 0.27 mmol) to give 15 34 mg of a purple solid. M+1 538.2 Calcd 538.15.

**EXAMPLE 58**

20

**N-{4-(1,4-diazepan-1-yl)-2-[(phenylsulfonyl)amino]phenyl}-2,4,6-trimethylbenzenesulfonamide hydrochloride (Scheme 3)**

The compound was synthesized from of N-{2-amino-5-(4-*t*-butyloxycarbonyl-1,4-diazepan-1-yl)- phenyl}benzenesulfonamide and 2-mesitylenesulfonylchloride (59 mg, 0.27 mmol) to give 25 56 mg as purple solid. M+1 529.3 Calcd 529.70;  $^1\text{H}$ NMR  $\delta$  7.80-7.47 (m, 5H), 6.93 (s br, 2H), 6.64 (d, 1H), 6.46-6.39 (m, 2H), 3.60 (app t, 2H), 3.39 (app t, 2H), 3.21 (app t, 2H), 3.12 (app t, 2H), 2.36 (s, 6H), 2.26 (s, 3H), 2.08-2.00 (m, 2H).

**EXAMPLE 59**

30

**N-{4-(1,4-diazepan-1-yl)-2-[(phenylsulfonyl)amino]phenyl}-4-methylbenzenesulfonamide hydrochloride (Scheme 3)**

The compound was synthesized from of N-{2-amino-5-(4-*t*-butyloxycarbonyl-1,4-diazepan-1-yl)- phenyl}benzenesulfonamide and p-toluenesulfonylchloride (51 mg, 0.27

mmol) to give 22 mg as purple solid. M+1 501.3 Calcd 501.15;  $^1\text{H}$ NMR  $\delta$  7.77-7.26 (m, 9H), 6.54 (d, 1H), 6.50 (d, 1H), 6.40 (dd, 1H), 3.63 (app t, 2H), 3.42 (app t, 2H), 3.25 (app t, 2H), 3.16 (app t, 2H), 2.38 (s, 3H), 2.11-2.03 (m, 2H).

5 EXAMPLE 60

**N-[5-(1,4-diazepan-1-yl)-2-({[(E)-2-phenylethenyl]sulfonyl}amino)phenyl]benzenesulfonamide hydrochloride (Scheme 3)**

The compound was synthesized from of N-{2-amino-5-(4-t-butyloxycarbonyl-1,4-diazepan-1-yl)- phenyl}benzenesulfonamide and beta-styrenesulfonylchloride (55 mg, 0.27 mmol) to give before Boc-deprotection 12 mg as purple solid. M+1 513.6 Calcd 512.15;  $^1\text{H}$ NMR  $\delta$  7.78-7.38 (m, 10H), 7.20 (d, 1H), J = 15.4 Hz), 7.10 (d, 1H), 6.98 (d, 1H), J = 15.4 Hz), 6.56 (dd, 1H), 6.44 (d, 1H), 3.62 (app t, 2H), 3.41 (app t, 2H), 3.23 (app t, 2H), 3.15 (app t, 2H), 2.09-2.01 (m, 2H).

15

EXAMPLE 61

**N-{4-(1,4-diazepan-1-yl)-2-[(phenylsulfonyl)amino]phenyl}-2,5-dimethoxybenzenesulfonamide hydrochloride (Scheme 3)**

The compound was synthesized from of N-{2-amino-5-(4-t-butyloxycarbonyl-1,4-diazepan-1-yl)-phenyl}benzenesulfonamide and 2,5-dimethoxybenzenesulfonylchloride (64 mg, 0.27 mmol) to give 14 mg as purple solid. M+1 547.3 Calcd 547.16;  $^1\text{H}$ NMR  $\delta$  7.71-7.00 (m, 9H), 6.48 (dd, 1H), 6.16 (d, 1H), 4.04 (s, 3H), 3.68 (s, 3H), 3.56 (app t, 2H), 3.33 (app t, 2H), 3.17 (app t, 2H), 3.11 (app t, 2H), 2.03-1.95 (m, 2H).

25

EXAMPLE 62

**N-{4-(1,4-diazepan-1-yl)-2-[(phenylsulfonyl)amino]phenyl}-2-methylbenzenesulfonamide hydrochloride (Scheme 3)**

30 The compound was synthesized from of N-{2-amino-5-(4-t-butyloxycarbonyl-1,4-diazepan-1-yl)- phenyl}benzenesulfonamide and o-toluenesulfonylchloride (51 mg, 0.269

mmol) to give 18 mg as purple solid. M+1 501.3 Calcd 501.15;  $^1\text{H}$ NMR  $\delta$  7.78-7.17 (m, 9H), 6.68-6.35 (m, 3H), 3.63-3.10 (m, 8H), 2.59 (s, 3H), 2.09-2.01 (m, 2H).

EXAMPLE 63

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**4-Butoxy-N-{4-(1,4-diazepan-1-yl)-2-[(phenylsulfonyl)amino]phenyl}-benzenesulfonamide hydrochloride (Scheme 3)**

The compound was synthesized from of N-{2-amino-5-(4-t-butyloxycarbonyl-1,4-diazepan-1-yl)- phenyl}benzenesulfonamide and 4-n-butoxybenzenesulfonylchloride (67 mg, 0.269 mmol) to give 27 mg as purple solid. M+1 559.4 Calcd 559.20;  $^1\text{H}$ NMR  $\delta$  7.77-7.47 (m, 7H), 6.96-6.93 (m, 2H), 6.55 (d, 1H), 6.52 (d, 1H), 6.41 (d, 1H), 4.01 (t, 2H), 3.63 (app t, 2H), 3.43 (app t, 2H), 3.25 (app t, 2H), 3.17 (app t, 2H), 2.11-2.03 (m, 2H), 1.80-1.71 (m, 2H), 1.53-1.45 (m, 2H), 0.98 (t, 3H).

15 EXAMPLE 64

**N-{4-(1,4-diazepan-1-yl)-2-[(phenylsulfonyl)amino]phenyl}-3,5-dimethyl-4-isoxazolesulfonamide hydrochloride (Scheme 3)**

The compound was synthesized from of N-{2-amino-5-(4-t-butyloxycarbonyl-1,4-diazepan-1-yl)- phenyl}benzenesulfonamide and 3,5-dimethylisoxazolesulfonylchloride (53 mg, 0.269 mmol) to give 32 mg as purple solid. M+1 506.3 Calcd 506.15;  $^1\text{H}$ NMR  $\delta$  7.75-7.48 (m, 5H), 6.92 (d, 1H), 6.59 (dd, 1H), 6.28 (d, 1H), 3.62 (app t, 2H), 3.41 (app t, 2H), 3.21 (app t, 2H), 3.12 (app t, 2H), 2.23 (s, 3H), 2.13 (s, 3H), 2.09-2.01 (m, 2H).

25 EXAMPLE 65

**N-{4-(1,4-diazepan-1-yl)-2-[(phenylsulfonyl)amino]phenyl}-5-fluoro-2-methylbenzenesulfonamide hydrochloride (Scheme 3)**

The compound was synthesized from of N-{2-amino-5-(4-t-butyloxycarbonyl-1,4-diazepan-1-yl)- phenyl}benzenesulfonamide and 5-fluoro-2-methylbenzenesulfonylchloride (56 mg, 0.269 mmole) to give 7 mg as purple solid. M+1 519.3 Calcd 519.15;  $^1\text{H}$ NMR  $\delta$

7.78-7.18 (m, 8H), 6.72 (d, 1H), 6.45 (dd, 1H), 6.34 (d, 1H), 3.59 (app t, 2H), 3.38 (app t, 2H), 3.21 (app t, 2H), 3.13 (app t, 2H), 2.57 (s, 3H), 2.06-1.98 (m, 2H).

#### EXAMPLE 66

5

#### N-{4-(1,4-diazepan-1-yl)-2-[(phenylsulfonyl)amino]phenyl}-4-(methylsulfonyl)benzenesulfonamide hydrochloride (Scheme 3)

The compound was synthesized from of N-{2-amino-5-(4-*t*-butyloxycarbonyl-1,4-diazepan-1-yl)- phenyl}benzenesulfonamide and 4-methylsulfonylbenzenesulfonylchloride 10 (69 mg, 0.269 mmole) to give 38 mg as purple solid. M+1 565.3 Calcd 565.12; <sup>1</sup>H NMR δ 8.08-7.48 (m, 9H), 6.76 (d, 1H), 6.48 (dd, 1H), 6.32 (d, 1H), 3.61 (app t, 2H), 3.38 (app t, 2H), 3.21 (app t, 2H), 3.17 (app t, 2H), 3.14 (app t, 2H), 2.08-2.00 (m, 2H).

#### EXAMPLE 67

15

#### N-{4-(1,4-diazepan-1-yl)-2-[(methylsulfonyl)amino]phenyl}-N-methylbenzenesulfonamide (Scheme 3)

N-methyl-{2-amino-5-(4-*t*-butyloxycarbonyl-1,4-diazepan-1-yl)- phenyl}-benzenesulfonamide (0.196 g, 0.426 mmol) was dissolved in pyridine (1.67 ml) followed by 20 the addition of methyl sulphonylchloride (57 mg, 0.50 mmol). The ractiom was stirred at rt for 3 h. The mixture was concentrated and treated with trifluoroacetic acid (50%) in DCM for 30 min then concentrated and left for our HPLC Separation specialists. Further purification by column cheomatography DCM/ MeOH (9:1) afforded 32 mg, 0.058 mmol in 13% yield of the title compound. <sup>1</sup>H NMR (CD<sub>3</sub>OD) δ 2.17 (m, 2 H), 3.05 (s, 3 H), 3.14 (s, 3 H), 3.27 (m, 2 H), 3.38 (m, 2 H), 3.57 (m, 2 H), 3.77 (m, 2 H), 6.28 (d, 1 H), 6.41 (dd, 1 H), 7.06 (d, 1 H), 7.65 (m, 5 H); <sup>13</sup>C NMR (CD<sub>3</sub>OD) δ 25.0, 38.7, 39.0, 45.1, 45.5, 45.8, 47.0, 100, 103.9, 108.1, 121.4, 125, 126, 128, 133.4, 136, 137.5, 148.5; M/Z Calc for (C<sub>19</sub>H<sub>26</sub>N<sub>4</sub>O<sub>4</sub>S<sub>2</sub>) 438.14 found M<sup>+</sup>+1=439.2

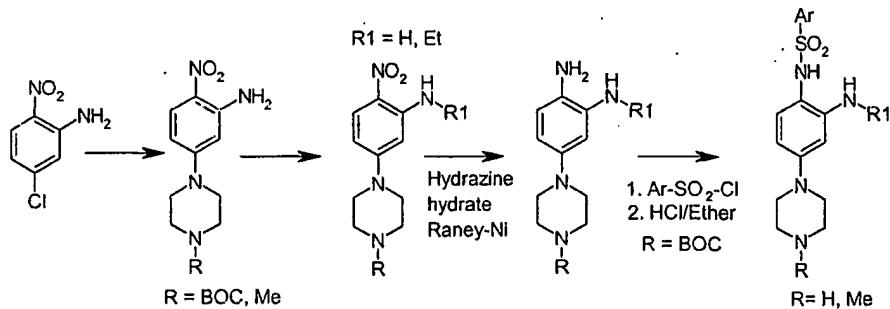
30 EXAMPLE 68

**N-{5-(1,4-diazepan-1-yl)-2-[methyl(phenylsulfonyl)amino]phenyl}-4-methylbenzenesulfonamide (Scheme 3)**

N-methyl-{2-amino-5-(4-*t*-butyloxycarbonyl-1,4-diazepan-1-yl)- phenyl}-benzenesulfonamide (0.196 g, 0.426 mmol) was dissolved in pyridine (1.67 ml) followed by 5 the addition of p-methylphenyl-sulphonylchloride (88 mg, 0.50 mmol) the reaction was stirred at rt for 3h. The mixture was concentrated and treated with trifluoroacetic acid (50%) in DCM for 30 min then concentrated and left for our HPLC Separation specialists. Further purificaction by flash column chromatography DCM / MeOH (9:1) afforded 0.110 g, 0.175 mmol in 40% yield of title compound. <sup>1</sup>H NMR (CD<sub>3</sub>OD) δ 2.17 (m, 2 H), 2.52, (s, 3H), 3.0-10 3.4 (m; 7 H), 3.52 (m, 2 H), 3.74 (m, 2 H), 6.15 (d, 1 H), 6.41 (d, 1 H), 6.92 (s, 1 H), 7.5-7.80 (m, 6 H); M/Z Calc for (C<sub>25</sub>H<sub>30</sub>N<sub>4</sub>O<sub>4</sub>S<sub>2</sub>) 514.1708 found M<sup>+</sup> 514.1708.

**General method for the preparation of monosulfonamides**

15 **Scheme 4**



**EXAMPLE 69**

20

**N-[2-Amino-4-(1-piperazinyl)phenyl]-3-fluorobenzenesulfonamide (Scheme 4)**

tert-Butyl 4-(3-amino-4-nitrophenyl)-1-piperazinecarboxylate (1.5 g, 3.5 mmol) was dissolved in methanol:THF (4:1). Raney-Ni (900 mg) was added followed by addition of hydrazine monohydrate (900 mg). The reaction was stirred at r. t. under N<sub>2</sub> atmosphere 25 overnight. Starting material was present. Raney-Ni (400 mg) was added and the reaction was stirred overnight. The reaction was filtered through celite pad followed by washings with

ethanol. The volatiles were evaporated to afford 93% of 2-amino-5-(4-t-butylcarboxyl-1-piperazinyl) aniline.

2-amino-5-(4-t-butylcarboxyl-1-piperazinyl) aniline (150 mg, 0.382 mmol) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (2 mL). 3-fluorophenylsulfonylchloride (74 mg, 0.382 mmol), pyridine (215 µL, 2.67 mmol) were added and the reaction was stirred at room temperature for 2 hr. The reaction was quenched with NaHCO<sub>3</sub> (saturated aqueous solution), extracted with CH<sub>2</sub>Cl<sub>2</sub>. The organic phase was dried (MgSO<sub>4</sub>), filtered and concentrated to give an oil residue that was purified by flash column chromatography (SiO<sub>2</sub>, CH<sub>3</sub>Cl:MeOH:NH<sub>3</sub> 10 9:1:0.4%) to afford of N-[2-amino-4-(4-tert-butylcarboxyl-1-piperazinyl)-3-fluorobenzenesulfonamide (80 %).

N-[2-amino-4-(4-tert-butylcarboxyl-1-piperazinyl)-3-fluorobenzenesulfonamide (110 mg) were dissolved in methanol (0.5 mL) followed by the addition of diethylether (2 mL). Ether/HCl gas was added till pH = 1. The reaction was stirred at room temperature for 5 h to afford the title product as a white solid <sup>1</sup>H NMR (methanol-d3) δ 3.25-3.50 (m, 8H); 6.5 (d, 1H); 6.75 (dd, 1H), 7.0 (bs, 1H); 7.3-7.6 (m, 4H); MS (posEI-DIP) m/z = 351.2 (M+H).

#### EXAMPLE 70

20

#### **N-[2-(ethylamino)-4-(4-methyl-1-piperazinyl)phenyl]-3-fluorobenzenesulfonamide hydrochloride (Scheme 4)**

To a solution of N-2-ethyl-4-(4-methyl-1-piperazinyl)-1,2-benzenediamine (0.200 g, 0.853 mmol) and pyridine (0.48 mL, 5.97 mmol) in DCM (8 mL) was added a solution of 3-fluorobenzenesulfonyl chloride (249 mg, 1.28 mmol) in DCM (2 mL). The mixture was stirred at room temperature for 16 hours. DCM (10 mL) was added and the mixture was washed with saturated aqueous NaHCO<sub>3</sub>. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. Column chromatography on Al<sub>2</sub>O<sub>3</sub> using EtOAc/5% MeOH as eluent gave two products. First fraction contains 110 mg of N-[2-{ethyl[(3-fluorophenyl)sulfonyl]amino}-4-(4-methyl-1-piperazinyl)phenyl]-3-fluorobenzenesulfonamide hydrochloride. Second fraction contains 100 mg of N-[2-

(ethylamino)-4-(4-methyl-1-piperazinyl)phenyl]-3-fluorobenzenesulfonamide hydrochloride. Both products were converted to the HCl-salts. N-[2-(ethylamino)-4-(4-methyl-1-piperazinyl)phenyl]-3-fluorobenzenesulfonamide hydrochloride:  $^1\text{H}$  NMR (DMSO-*d*6)  $\delta$  11.24 (br s, 1H), 9.76 (br s, 1H), 7.66-7.59 (m, 1H), 7.56-7.50 (m, 3 H), 6.62 (app d,  $J=8.8$  Hz, 1H), 6.55-6.35 (m, 2H), 3.80-3.70 (m, 2 H), 3.46-3.40 (m, 2H), 3.15-2.96 (m, 6H), 2.76 (app d,  $J=4.4$  Hz, 3H), 1.08 (tr,  $J=7.2$  Hz, 3H);  $^{13}\text{C}$  NMR (CD<sub>3</sub>OD)  $\delta$  161.03 (d,  $J_{\text{CF}}=248$  Hz), 149.32, 142.13 (d,  $J_{\text{CF}}=6.4$  Hz), 140.72, 131.43 (d,  $J_{\text{CF}}=7.4$  Hz), 128.56, 123.22, 119.93 (d,  $J_{\text{CF}}=20$  Hz), 115.91, 113.86 (d,  $J_{\text{CF}}=24$  Hz), 107.78, 103.12, 51.83, 45.04, 41.80, 40.62, 12.88; AccMs (posES-FIA) found: 392.1672, calc: 392.1782; Ms (posES-FIA) *m/z* 393 (M+H).

#### EXAMPLE 71

##### 4-Chloro-N-[5-(4-methyl-1,4-diazepan-1-yl)-2-nitrophenyl]benzenesulfonamide

###### (Scheme 4)

4-chlorobenzene sulfonamide (3.5 g, 18.3 mmol) was added slowly to a suspension of sodium hydride (1.6 g, 55% suspension in mineral oil, 36.6 mmol) in anhydrous DMF (50 mL) under an atmosphere of nitrogen. The mixture was warmed to 40°C for 1 hour and 2,4-difluoronitrobenzene (2 mL) was added dropwise. This mixture was stirred at 60°C overnight. The cooled reaction mixture was poured into hydrochloric acid (1 N, 250 mL) and extracted with ethyl acetate (2 x 50 mL). The organic extracts were washed with water, dried over MgSO<sub>4</sub> and evaporated to give a yellow solid. The product was re-crystallized from ethanol. Yield 2.4g (40%).  $^1\text{H}$  NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  6.85 (m, 1 H), 7.48 (AB,  $J = 8.3$  Hz, 2 H), 7.56 (dd,  $J = 10.01, 2.68$  Hz, 1 H), 7.84 (AB,  $J = 8.3$  Hz, 2 H), 8.21 (dd,  $J = 9.28, 5.61$  Hz, 1 H), 10 (bs, 1 H). Calculated N 8.47%, C 43.58%, S 9.70%, H 2.44%; Found N 8.54%, C 43.89%, S 10.10%, H 2.76%. 4-Chloro-N-[5-fluoro-2-nitrophenyl]benzenesulfonamide (1g, 3mmol) and N-methylhomopiperazine (0.4mL) were heated together at 130 °C for 3 hours. The product was allowed to cool, dissolved in CH<sub>2</sub>Cl<sub>2</sub> (50 mL) and washed with aqueous sodium bicarbonate. The organic phase was dried over MgSO<sub>4</sub> and evaporated to give 1.05 g of a yellow solid which was re-crystallized from toluene. Yield 0.65g (51%).  $^1\text{H}$  NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  1.98 (q,  $J = 5.62$  Hz, 1 H), 2.37

(s, 3 H), 2.52 (t,  $J$  = 5.62 Hz, 2 H), 2.67 (t,  $J$  = 5.12 Hz, 2 H), 3.55 (t,  $J$  = 6.35 Hz, 2 H), 3.60 (t,  $J$  = 5.12 Hz, 2 H), 6.34 (dd,  $J$  = 9.77, 2.68 Hz, 1 H), 6.86 (d,  $J$  = 2.68 Hz, 1 H), 7.43 (ab,  $J$  = 8.79 Hz, 2 H), 7.79 (ab,  $J$  = 8.79 Hz, 2 H), 8.01 (d,  $J$  = 9.77 Hz, 1 H), 11.6 (br s, 1 H). Calculated N 13.19%, C 50.88%, H 4.98%; Found N 13.27%, C 50.99%, H 4.83%.

5

## EXAMPLE 72

**N-[2-amino-5-(1,4-diazepan-1-yl)phenyl]benzenesulfonamide (Scheme 4)**

N-{5-(4-t-butyloxycarbonyl-1,4-diazepan-1-yl)-2-nitro-phenyl}benzenesulfonamide (1.85 g, 3.88 mmol) was dissolved in EtOH/THF (1:4). Hydrazine (0.970 mL, 19.4 mmol) and Raney-Ni (0.180 g) was added. After 1 h at room temperature, the reaction was filtered through wet celite and the solvent was removed to afford 1.71 g of colorless oil. Boc-deprotection was achieved by dissolving N-{5-(4-t-butyloxycarbonyl-1,4-diazepan-1-yl)-2-amino-phenyl}benzenesulfonamide (0.039 g) in small amount of MeOH and adding HCl/ether. The mixture was left at room temperature for 0.5 h after which the solvent was removed. Re-crystallization from MeOH/ether gave PHA-509592A (23 mg) as a white solid. M+1 347.4 Calcd 347.15;  $^1\text{H}$ -NMR  $\delta$  7.73-7.54 (m, 5H), 7.30 (d, 1H), 6.84 (dd, 1H), 5.78 (d, 1H), 3.55 (app t, 2H), 3.32-3.26 (m, 2H), 3.13-3.08 (m, 4H), 2.03-1.92 (m, 2H).

20 EXAMPLE 73

**N-[2-amino-5-(4-methyl-1,4-diazepan-1-yl)phenyl]benzenesulfonamide hydrochloride (Scheme 4)**

The above sulfonamide (0.6 g, 1.8 mmol) in methanol (50 mL) with Palladium (10% on C, 0.3g) was hydrogenated at atmospheric pressure for one hour during which time 140 mL of hydrogen was consumed. The solution was filtered and evaporated to give colorless oil. The oil was dissolved in toluene (20 mL) and treated with a solution of hydrogen chloride in ethyl acetate. The product was triturated with cyclohexane, collected by filtration and dried. Yield 0.44g (73%). A portion was recrystallized from toluene:ethanol 1:1.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.95 (br, 1 H), 2.17 (br, 1 H), 2.72 (s, 3 H), 2.80-3.65 (br m, 8 H), 5.92 (br, 1 H), 6.66 (dd,  $J$  = 2.69, 9.03 Hz, 1 H), 7.20 (d,  $J$  = 9.03 Hz, 1 H), 7.63 (t,  $J$  = 7.81

Hz, 2 H), 7.71 (t,  $J$  = 7.32 Hz, 1 H), 7.81 (d,  $J$  = 7.32 Hz, 2 H), 9.8 (br, 3 H), 11 (br s, 1 H).  
MS (ESI+) for  $C_{18}H_{24}N_4O_2S$   $m/z$  360.1634 ( $M^+$ )<sup>+</sup> (Calculated 360.1620)

#### EXAMPLE 74

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##### N-[4-Nitro-3-(1-piperazinyl)phenyl]benzenesulfonamide hydrochloride (Scheme 4)

A mixture of difluoronitrobenzene (1.31 g, 8.21 mmol), Boc-piperazine (1.84 g, 9.8 mmol) and  $K_2CO_3$  in DMF was stirred at room temperature overnight. The mixture was filtered and the DMF was removed. The residue was dissolved in  $CH_2Cl_2$  and extracted with HCl (1M) three times. The organic layers were dried ( $MgSO_4$ ), filtered and the solvent was removed. Purification by column chromatography ( $SiO_2$ ,  $CH_2Cl_2/heptane$ , 1:4) gave 1.14 g of yellow solid.  $^1H$ -NMR  $\delta$  7.90 (dd, 1H), 6.77-6.69 (m, 2H), 3.60-3.57 (m, 4H), 3.03-3.00 (m, 4H), 1.46 (s, 9H); MS (posEI-DIP)  $m/z$  = Found: 348.2 ( $M^+ + Na^+$ ).  $NaH$  (17.2 mg, 0.43 mmol) was added to a solution of 4-(2-nitro-5-fluorophenyl)-1-(*t*-butyloxycarbonyl)piperazine (0.079 g, 0.215 mmol) and benzensulfonamide (0.044g, 0.280 mmol) in DMF. The mixture was heated at 80°C over night and filtered. Purification by column chromatography ( $SiO_2$ ,  $CH_2Cl_2/heptane$ , 1:4) gave 0.075 g of N-[2-nitro-4-(*t*-butyloxycarbonylpiperazinyl)]phenyl]benzenesulfonamide of which 0.025 mg was Boc-deprotected by dissolving the compound in MeOH and adding HCl/ether. The mixture was stirred for 0.5 h after which the solvent was removed. Re-crystallization MeOH/ether gave 24.6 mg of a yellow solid.  $^1H$ -NMR  $\delta$  7.88 (app d, 3H), 7.63-7.52 (m, 3H), 7.07 (d, 1H), 6.89 (dd, 1H), 3.38-3.34 (m, 4H), 3.25-3.21 (m, 4H); MS (posEI-DIP)  $m/z$  = Found: 363.3 ( $M^+ + H^+$ ).

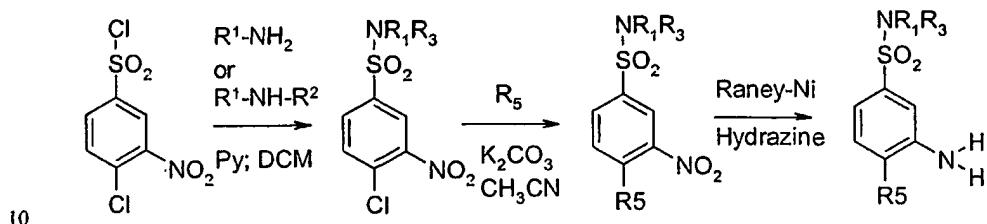
25

#### EXAMPLE 75

##### N-[4-amino-3-(1-piperazinyl)phenyl]benzenesulfonamide hydrochloride (Scheme 4)

To a solution of N-[2-nitro-4-(*t*-butyloxycarbonylpiperazinyl)]phenyl]benzenesulfonamide (50 mg, 0.108 mmol) in THF/EtOH 4:1 was added Raney-Ni (5 mg) and hydrazine hydrate (27  $\mu$ L, 0.54 mmol). The mixture was stirred at room temperature for 6 h followed by filtration of the reaction mixture through wet Celite. Removal of the solvent and

purification by column chromatography ( $\text{SiO}_2$ ,  $\text{CH}_2\text{Cl}_2/\text{heptane}/\text{MeOH}$ , 4:5:1) gave N-[2-amino-4-(t-butyloxycarbonyl-piperazinyl)]phenyl]-benzenesulfonamide. Boc-deprotection was achieved by dissolving the compound in MeOH and adding HCl/ether. The mixture was stirred for 0.5 h after which the solvent was removed. Re-crystallization (MeOH/ether) gave 5 a white solid that had to be purified by preparative HPLC to obtain 10 mg of the final product.  $^1\text{H-NMR}$   $\delta$  7.66-7.45 (m, 5H), 6.78 (d, 1H), 6.62 (d, 1H), 6.50 (dd, 1H), 3.39-3.35 (m, 4H), 3.02-2.99 (m, 4H); MS (posEI-DIP) m/z = Found: 333.0 ( $\text{M}^+ + \text{H}^+$ ).

**Scheme 5****Method 5**

10 4-Chloro-3-nitrobenzenesulfonyl chloride, taken from a prepared stock solution, (1.78 mmol, 1.0 eq) in  $\text{CH}_2\text{Cl}_2$  (2 mL) was added to a solution of the appropriate  $\text{R}^n$ -15 substituted anilines ( $\text{R}^1\text{-NH}_2$  or  $\text{R}^1\text{-NH-}\text{R}^3$ ) (1.62 mmol, 1.0 equiv.) in the presence of pyridine (11.34 mmol, 7.0 equiv.).

The reactions were stirred overnight at room temperature. Each mixture was washed 20 with 1N HCl followed by  $\text{NaHCO}_3$  (sat. aqueous). Each organic phase was separated, dried ( $\text{Na}_2\text{SO}_4$ ), and filtered.  $\text{CH}_2\text{Cl}_2$  (2 mL) were added to each reaction mixture followed by the addition of  $\text{K}_2\text{CO}_3$  (3.24 mmol, 2.0 equiv.) and homopiperazine or other amines of choice (i.e.  $\text{R}^5$ ) (2.11 mmol, 1.3 equiv.). Each reaction mixture was stirred at room temperature for 2 days. The volatiles were eliminated using a speed vac. Each reaction mixture was dissolved 25 in a 4:1 EtOH:THF (25 mL) followed by addition of Raney-Ni (0.5 mL suspension in EtOH) and hydrazine monohydrate (8.10 mmol, 5.0 equiv.). Each mixture was stirred at room temperature for 2 days and then filtered (Celite pad pretreated with water). The filtrates were concentrated to give the crude products (LC-MS). An aliquot of each reaction mixture was

purified by reversed phase preparative HPLC to give analytical samples which were converted to their HCl-salts and sent for pharmacological testing.

#### EXAMPLE 76

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##### **3-Amino-4-(1,4-diazepan-1-yl)-N-(4-methoxyphenyl)benzenesulfonamide hydrochloride (Scheme 5, Method 5)**

The compound was prepared from p-anisidine; (crude yield 0.238 g, yield analytical pure sample 0.137 g);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.43-7.39 (m, 2H), 7.37-7.33 (m, 1H), 7.00-6.96 (m, 2H), 6.78-6.74 (m, 2H), 3.71 (s, 3H), 3.47-3.38 (m, 6H), 3.17-3.13 (m, 2H), 2.19-2.12 (m, 2H); MS (posESI) m/z = 377 ( $\text{M}+\text{H}^+$ ).

#### EXAMPLE 77

15    **3-Amino-4-(1,4-diazepan-1-yl)-N-(3-methoxyphenyl)benzenesulfonamide hydrochloride  
(Scheme 5, Method 5)**

The compound was prepared from m-anisidine; (crude yield 0.546 g, yield analytical pure sample 0.020 g);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.71-7.67 (m, 2H), 7.51-7.47 (m, 1H), 7.12-7.07 (m, 1H), 6.72-6.69 (m, 1H), 6.68-6.65 (m, 1H), 6.63-6.59 (m, 1H), 3.71 (s, 3H), 3.48-3.40 (m, 6H), 3.18-3.14 (m, 2H), 2.21-2.15 (m, 2H); MS (posES-FIA) m/z = 377 ( $\text{M}+\text{H}^+$ ).

#### EXAMPLE 78

25    **3-Amino-4-(1,4-diazepan-1-yl)-N-(2-methoxyphenyl)benzenesulfonamide hydrochloride  
(Scheme 5, Method 5)**

The compound was prepared from o-anisidine; (crude yield 0.469 g, yield analytical pure sample 0.010 g);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.51-7.47 (m, 2H), 7.42-7.35 (m, 2H), 7.11-7.06 (m, 1H), 6.89-6.82 (m, 2H), 3.57 (s, 3H), 3.47-3.38 (m, 6H), 3.17-3.12 (m, 2H), 2.20.2.13 (m, 2H); MS (posES-FIA) m/z = 377 ( $\text{M}+\text{H}^+$ ).

30

## EXAMPLE 79

**3-Amino-4-(1,4-diazepan-1-yl)-N-(3-fluorophenyl)benzenesulfonamide hydrochloride  
(Scheme 5, Method 5)**

5 The compound was prepared from 3-fluoroaniline; (crude yield 0.580 g, yield analytical pure sample 0.043 g);  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  7.58-7.49 (m, 2H), 7.41-7.35 (m, 1H), 7.23-7.17 (m, 1H), 6.93-6.87 (m, 2H), 6.79-6.73 (m, 1H), 3.46-3.37 (m, 6H), 3.17-3.13 (m, 2H), 2.20-2.12 (m, 2H); MS (posES-FIA) m/z = 365 ( $\text{M}+\text{H}^+$ ).

## 10 EXAMPLE 80

**3-Amino-4-(1,4-diazepan-1-yl)-N-methyl-N-phenylbenzenesulfonamide hydrochloride  
(Scheme 5, Method 5)**

15 The compound was prepared from N-methylaniline; (crude yield 0.590 g, yield analytical pure sample 0.010 g);  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  7.41-7.36 (m, 1H), 7.35-7.22 (m, 5H), 7.15-7.11 (m, 2H), 3.50-3.44 (m, 6H), 3.23-3.17 (m, 5H), 2.33-2.16 (m, 2H); MS (posEI) m/z = 360 ( $\text{M}+\text{H}^+$ ).

## EXAMPLE 81

20 3-Amino-4-(1,4-diazepan-1-yl)-N-(4-isopropylphenyl)benzenesulfonamide  
hydrochloride (Scheme 5, Method 5)

The compound was prepared from 4-isopropylaniline; (crude yield 0.600 g, yield analytical pure sample 0.015 g);  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  7.48-7.41 (m, 2H), 7.35-7.31 (m, 1H), 7.10-7.05 (m, 2H), 7.03-6.98 (m, 2H), 3.47-3.35 (m, 6H), 3.17-3.12 (m, 2H), 2.80 (sept,  $J$  = 6.8 Hz, 1H), 2.20-2.10 (m, 2H), 1.17 (d,  $J$  = 6.8 Hz, 6H); MS (posEI) m/z = 388 ( $\text{M}+\text{H}^+$ ).

## EXAMPLE 82

30 3-Amino-4-(1,4-diazepan-1-yl)-N-(4-methylphenyl)benzenesulfonamide hydrochloride  
(Scheme 5, Method 5)

The compound was prepared from p-toluidine; (crude yield 0.590 g, yield analytical pure sample 0.020 g);  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  7.35-7.33 (m, 1H), 7.31-7.27 (m, 1H), 7.25-7.22 (m, 1H), 7.03-6.94 (m, 4H), 3.47-3.30 (m, partly obscured by solvent signal, 6H), 3.16-3.11 (m, 2H), 2.23 (s, 3H), 2.17-2.10 (m, 2H); MS (posESI) m/z = 360 ( $\text{M}+\text{H}^+$ ).

5

#### EXAMPLE 83

**3-Amino-4-(1,4-diazepan-1-yl)-N-(2,5-dimethylphenyl)benzenesulfonamide hydrochloride (Scheme 5, Method 5)**

10 The compound was prepared from 2,4-dimethylaniline; (crude yield 0.306 g, yield analytical pure sample 0.015 g);  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  7.33-7.28 (m, 3H), 6.99-6.95 (m, 1H), 6.93-6.88 (m, 2H), 3.50-3.37 (m, 6H), 3.19-3.14 (m, 2H), 2.22-2.13 (m, 5H), 1.96 (s, 3H); MS (posES-FIA) m/z = 375 ( $\text{M}+\text{H}^+$ ).

15 EXAMPLE 84

**3-Amino-N-(3-chlorophenyl)-4-(1,4-diazepan-1-yl)benzenesulfonamide hydrochloride (Scheme 5, Method 5)**

20 The compound was prepared from 3-chloroaniline; (crude yield 0.610 g, yield analytical pure sample 0.015 g);  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  7.25-7.24 (m, 1H), 7.19-7.14 (m, 3H), 7.12-7.10 (m, 1H), 7.04-6.99 (m, 2H), 3.45-3.30 (m, partly obscured by solvent signal, 6H), 3.15-3.11 (m, 2H), 2.14-2.08 (m, 2H); MS (posES-FIA) m/z = 381 ( $\text{M}+\text{H}^+$ ).

#### EXAMPLE 85

25

**3-Amino-4-(1,4-diazepan-1-yl)-N-(2-chlorophenyl)benzenesulfonamide hydrochloride (Scheme 5, Method 5)**

30 The compound was prepared from 2-chloroaniline; (crude yield 0.506 g, yield analytical pure sample 0.020 g);  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  7.55-7.50 (m, 1H), 7.40-7.20 (m, 5H), 7.15-7.10 (m, 1H), 3.48-3.34 (m, 6H), 3.18-3.12 (m, 2H), 2.20-2.10 (m, 2H); MS (posEI) m/z = 381 ( $\text{M}+\text{H}^+$ ).

**EXAMPLE 86****3-Amino-N-(2,4-dichlorophenyl)-4-(1,4-diazepan-1-yl)benzenesulfonamide****5 hydrochloride (Scheme 5, Method 5)**

The compound was prepared from 2,4-dichloroaniline; (crude yield 0.446 g, yield analytical pure sample 0.080 g);  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  7.53-7.50 (m, 1H), 7.37-7.35 (m, 1H), 7.32-7.27 (m, 2H), 7.25-7.23 (m, 2H), 3.48-3.37 (m, 6H), 3.18-3.12 (m, 2H), 2.20-2.10 (m, 2H); MS (posEI) m/z = 415 ( $\text{M}+\text{H}^+$ ).

10

**EXAMPLE 87****3-Amino-N-(2-methyl-5-chloro-phenyl)-4-(1,4diazepan-1-yl)benzenesulfonamide****hydrochloride (Scheme 5, Method 5)**

15 The compound was prepared from 2-methyl-5-chloroaniline; (crude yield 0.516 g, yield analytical pure sample 0.015 g);  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  7.47-7.34 (m, 3H), 7.16-7.13 (m, 1H), 7.10 (-7.04 (m, 2H), 3.48-3.39 (m, 6H), 3.20-3.15 (m, 2H), 2.21-2.14 (m, 2H); MS (posESI) m/z = 395 ( $\text{M}+\text{H}^+$ ).

20 EXAMPLE 88

**3-Amino-N-(2-methyl-3-chloro-phenyl)-4-(1,4-diazepan-1-yl)benzenesulfonamide****hydrochloride (Scheme 5, Method 5)**

25 The compound was prepared from 2-methyl-3-chloroaniline; (crude yield 0.537 g, yield analytical pure sample 0.22 g);  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  7.40-7.34 (m, 3H), 7.26-7.23 (m, 1H), 7.08-6.99 (m, 2H), 3.50-3.38 (m, 6H), 3.20-3.16 (m, 2H), 2.21-2.14 (m, 2H) 2.11 (s, 3H); MS (posESI) m/z = 395 ( $\text{M}+\text{H}^+$ ).

**EXAMPLE 89****3-Amino-N-(4-trifluoro-phenyl)-4-(1,4-diazepan-1-yl)benzenesulfonamide hydrochloride (Scheme 5, Method 5)**

5       The compound was prepared from 4-trifluoroaniline; (crude yield 0.319 g, yield analytical pure sample 0.013 g);  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  7.53-7.45 (m, 2H), 7.27-7.22 (m, 3H), 7.13-7.08 (m, 2H), 3.43-3.30 (m, partly obscured by solvent signal, 6H), 3.14-3.09 (m, 2H), 2.12-2.06 (m, 2H); MS (posESI) m/z = 415 ( $\text{M}+\text{H}^+$ ).

**EXAMPLE 90**

10      **3-Amino-N-(4-fluorophenyl)-4-(1,4diazepan-1-yl)benzenesulfonamide hydrochloride (Scheme 5, Method 5)**

The compound was prepared from 4-fluoroaniline; (crude yield 0.700 g, yield analytical pure sample 0.021 g);  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  7.13-7.04 (m, 4H), 7.03-6.98 (m, 1H), 15 6.97-6.91 (m, 2H), 3.45-3.30 (m, partly obscured by solvent signal, 6H), 3.15-3.09 (m, 2H); MS (posEI) m/z = 365 ( $\text{M}+\text{H}^+$ ).

**EXAMPLE 91**

20      **3-Amino-N-(2-fluorophenyl)-4-(1,4diazepan-1-yl)benzenesulfonamide hydrochloride (Scheme 5, Method 5)**

The compound was prepared from 2-fluoroaniline; (crude yield 0.646 g, yield analytical pure sample 0.080 g);  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  7.48-7.43 (m, 1H), 7.36-7.34 (m, 1H), 7.36-7.27 (m, 1H), 7.25-7.21 (m, 1H), 7.15-7.05 (m, 2H), 7.02-6.95 (m, 1H), 3.46-3.34 (m, 25 6H), 3.17-3.12 (m, 2H), 2.16-2.10 (m, 2H) ; MS (posESI) m/z = 365 ( $\text{M}+\text{H}^+$ ).

**EXAMPLE 93**

30      **4-(1,4-Diazepan-1-yl)-3-nitro-N-benzenesulfonamide hydrochloride (Scheme 5, Method 5)**

4-Chloro-3-nitro-N-benzenesulfonamide (1.52 g, 4.87 mmol), K<sub>2</sub>CO<sub>3</sub> (1.01 g, 7.3 mmol) and homopiperazine (0.585 g, 5.8 mmol) in CH<sub>3</sub>CN (100 mL) was heated to 70°C for 2h. The mixture was filtered and the solvent was removed. Column chromatography (CH<sub>2</sub>Cl<sub>2</sub>/MeOH/heptane 4:1:5 x 0.2 % NH<sub>3</sub>) gave 1.34 g of 4-(1,4-diazepan-1-yl)-3-nitro-N-benzenesulfonamide together with 0.152 g of the dialkylated product. The product (0.040 g) was transferred to its HCl-salt to give 0.038 g of the final product. Anal. (C<sub>17</sub>H<sub>21</sub>ClN<sub>4</sub>O<sub>4</sub>S x 0.5H<sub>2</sub>O) C, H, N.; MS (posESI) m/z = 377.4 (M+H<sup>+</sup>).

#### EXAMPLE 94

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##### **3-Amino-4-(1,4-diazepan-1-yl)-N-phenylbenzenesulfonamide hydrochloride (Scheme 5, Method 5)**

4-(1,4-Diazepan-1-yl)-3-nitro-N-phenylbenzenesulfonamide (0.599 g, 1.6 mmol) was dissolved in EtOH/THF (1:4). Hydrazine (0.398 mL, 8.0 mmol) and Raney-Ni (0.060 g) were added. After 1 h at room temperature the reaction was filtered through wet celite and the solvent was removed. The product was transferred to its HCl-salt by dissolving it in MeOH and adding HCl/ether. The solvent was removed and re-crystallized from (MeOH/ether) to give 0.537 g of a white solid. Anal. (C<sub>17</sub>H<sub>21</sub>ClN<sub>4</sub>O<sub>4</sub>S x 1.5H<sub>2</sub>O) C, H, N.; MS (posESI) m/z = 347.4 (M+H<sup>+</sup>).

20

#### EXAMPLE 92

##### **3-Amino-4-(4-methyl-1,4-diazepan-1-yl)-N-phenylbenzenesulfonamide (Scheme 5, Method 5)**

4-Chloro-3-nitrobenzenesulfonyl chloride (460 mg, 1.8 mmol) was added to a colorless solution of aniline (250 mg, 2.7 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) followed by pyridine (0.80 mL, 10.0 mmol). The resulting orange solution was stirred at room temperature for 30 minutes, after which time the mixture was concentrated under vacuum. Acidification with 2M aq. HCl followed by extraction using EtOAc and drying with Na<sub>2</sub>SO<sub>4</sub> followed by filtration through a plug of silica, gave 500 mg (62%) of 4-chloro-3-nitro-N-phenylbenzenesulfonamide. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 8.30 (d, 1H), 7.80 (dd, 2H), 7.55 (d, 1H),

7.20 (m, 5H). MS(negESI) m/z = 311(M- H<sup>+</sup>). 1-Methylhomopiperazine (258 mg, 2.3 mmol) was added to a solution of 4-chloro-3-nitro-N-phenylbenzenesulfonamide obtained as above (500 mg, 1.6 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (20 mL) followed by addition of K<sub>2</sub>CO<sub>3</sub> (310 mg, 2.3 mmol). The reaction mixture was heated to reflux. After 2.5 h, the solution was concentrated under 5 vacuum. After adjusting to pH = 6, the product was extracted using EtOAc to give, after drying with Na<sub>2</sub>SO<sub>4</sub> and concentration, 450 mg (72%) of 4-(4-methyl-1,4-diazepan-1-yl)-3-nitro-N-phenylbenzenesulfonamide as an orange oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 8.15 (d, 1H), 7.60 (dd, 1H), 7.15 (m), 6.95 (d, 1H), 3.45 (m, 2H), 3.30 (m, 2H), 2.75 (m, 2H), 2.60 (m, 2H), 2.35 (s, 3H), 1.95 (m, 2H). MS (posESI) m/z = 391(M+H<sup>+</sup>). To a solution of 4-(4-methyl-10 1,4-diazepan-1-yl)-3-nitro-N-phenylbenzenesulfonamide (225 mg, 0.58 mmol) in EtOH/THF (4/1, 25 mL) activated Raney-Ni (slurry in EtOH) and hydrazine monohydrate (142 μL, 2.9 mmol) were added. After stirring for 30 minutes at room temperature, the mixture was filtered and the yellow solution concentrated to give yellow oil. The oil was dissolved in a mixture diethyl ether/EtOAc followed by addition of excess of HCl/ether. The resulting 15 precipitate was filtered and washed with ether to give, after drying under vacuum at 40°C, 88 mg (38%) of 3-amino-4-(4-methyl-1,4-diazepan-1-yl)-N-phenylbenzenesulfonamide as a beige solid: Mp 84-85°C. MS (posESI) m/z = 361 (M+H<sup>+</sup>). <sup>1</sup>H NMR (MeOH-d3) δ 7.85 (d, 2H), 7.60 (d, 1H), 7.15 (m, 5H), 3.50 (m, 7H), 3.15 (m, 2H), 3.00 (s, 3H), 2.30 (m, 1H), 2.20 (m, 1H). Anal. (C<sub>18</sub>H<sub>24</sub>N<sub>4</sub>SO<sub>2</sub>.2HCl) C, H, N, S.

20

#### EXAMPLE 98

##### **3-Amino-N-(3-chlorophenyl)-4-(4-methyl-1-piperazinyl)benzenesulfonamide hydrochloride (Scheme 5, Method 5)**

25 A mixture of 4-chloro-3-nitrobenzenesulfonylchloride (1g, 3.9 mmol), 3-chloroaniline (0.5 mL, 4.7 mmol) and pyridine (1.6 mL) in CH<sub>2</sub>Cl<sub>2</sub> (2 mL) was stirred at room temperature. The reaction was quenched with NaHCO<sub>3</sub> (sat aq solution, 30 mL x 3). The organic phase was separated, dried (MgSO<sub>4</sub>), and filtered. The volatiles were evaporated and the residue was purified by column chromatography (SiO<sub>2</sub>, pentane:EtOAc, 4:1) to give 30 4-chloro-N-(3-chlorophenyl)-3-nitrobenzenesulfonamide; MS (posESI) m/z = 349.2 (M+H<sup>+</sup>). <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.00-7.40 (m, 3H), 7.60-7.90 (m, 3H), 8.70 (bs, 1H). 4-Chloro-N-(3-

chlorophenyl)-3-nitrobenzenesulfonamide (0.45 g, 1.3 mmol), N-methylpiperazine (0.191 mL, 1.73 mmol) and K<sub>2</sub>CO<sub>3</sub> (359 mg, 2.6 mmol) in CH<sub>3</sub>CN (2.5 mL) as the filtrated was concentrated to give a residue which was purified by column (SiO<sub>2</sub>, CHCl<sub>3</sub>:MeOH: NH<sub>3</sub> 9:1:0.4 %) to give 420 mg of N-(3-chlorophenyl)-4-(4-methyl-1-piperazinyl)-3-nitrobenzenesulfonamide (85 %). Purity >95 % according to HPLC analysis. The compound was dissolved in THF (1 mL) and ethanol (5 mL) was added. The solution was treated with Raney-Ni (50 mg) and hydrazine monohydrate (0.05 mL) overnight. The Raney-Ni was filtered (celite pad), the volatiles were evaporated and the residue was purified by column chromatography (SiO<sub>2</sub>, CHCl<sub>3</sub>:MeOH: NH<sub>3</sub> 9:1:0.4 %). The product was isolated as hydrochloride salt by treatment with HCl gas in diethyl ether to yield 170 mg of final product (32 %).

<sup>1</sup>H NMR (DMSO-d6) δ 7.25 (appt, 1H), 7.15-7.17 (m, 1H), 7.10-6.12 (m, 1H), 7.00-7.10 (m, 4H); 3.43-3.45 (m, 2H), 3.22-3.24 (m, 4H), 2.96-3.01 (m, 2H), 2.77-2.78 (s, 3H); MS (posESI) m/z = 380.1(M+H<sup>+</sup>).

15

#### EXAMPLE 99

##### **3-Amino-N-(2-methoxyphenyl)-4-(4-methyl-1-piperazinyl)benzenesulfonamide hydrochloride (Scheme 5, Method 5)**

20 The compound was prepared from 4-chloro-3-nitrobenzenesulfonylchloride (1g, 3.9 mmol), 2-methoxyaniline (0.53 mL, 4.7 mmol) and pyridine (1.6 mL) in CH<sub>2</sub>Cl<sub>2</sub> (2 mL). 4-Chloro-N-(2-methoxyphenyl)-3-nitrobenzenesulfonamide (0.345 mg) was reacted with N-methylpiperazine (0.144 mL) to afford N-(2-methoxyphenyl)-4-(4-methyl-1-piperazinyl)-3-nitrobenzenesulfonamide which was treated with Raney-Ni and hydrazine monohydrate. The 25 final product was isolated as its HCl salt <sup>1</sup>H NMR (DMSO-d6) δ 7.185 (dd, 1H), 7.08 (dt, 1H), 6.975 (d, 1H), 6.91-6.94 (m, 2H); 6.84 (dt, 1H), 3.56 (s, 3H), 3.42-3.47 (m, 2H), 3.22-3.24 (m, 2H), 2.95 (bt, 2H), 2.79 (bs, 3H); MS (posESI) m/z = 376.2 (M+H<sup>+</sup>).

#### EXAMPLE 100

30

**3-Amino-N-(2-methoxyphenyl)-4-(1-piperazinyl)benzenesulfonamide hydrochloride  
(Scheme 5, Method 5)**

The compound was prepared from 4-chloro-3-nitrobenzenesulfonyl chloride (1 g, 3.9 mmol), 2-methoxyaniline (0.53 mL, 4.7 mmol) and pyridine (1.6 mL) in CH<sub>2</sub>CL<sub>2</sub> (2 mL). 4-5 Chloro-N-(2-methoxyphenyl)-3-nitrobenzenesulfonamide (0.345 g) was reacted with piperazine (0.111 g) to afford N-(2-methoxyphenyl)-4-(piperazinyl)-3-nitrobenzenesulfonamide. This was then treated with Raney-Ni and hydrazine monohydrate. The final product was isolated as its HCl salt. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ 7.18-7.20 (m, 1H), 7.08-7.10 (m, 2H), 6.93-6.96 (m, 1H), 6.91-6.93 (m, 2H); 6.84 (dt, 1H), 3.56 (s, 3H), 3.22-10 3.27 (m, 4H), 3.00-3.02 (m, 4H); MS (posESI) m/z = 362.1 (M+H<sup>+</sup>).

**EXAMPLE 95**

**2-(1,4-diazepan-1-yl)-5-(4-morpholinylsulfonyl)aniline hydrochloride (Scheme 5,  
15 Method 5)**

A suspension of homopiperazine (0.196 g, 1.95 mmol), 4-[(4-chloro-3-nitrophenyl)sulfonyl]morpholine (0.461 g, 1.50 mmol) and K<sub>2</sub>CO<sub>3</sub> (0.415 g, 3.00 mmol) in CH<sub>3</sub>CN (10 mL) was stirred at 65 °C for 16 h. CH<sub>2</sub>CL<sub>2</sub> (10 mL) was added and the mixture was filtered and concentrated. The crude product was purified by column chromatography on 20 silica using CHCl<sub>3</sub>→CHCl<sub>3</sub>/10% MeOH + 0.4% aqueous ammonia to yield 0.546 g of the product as a yellow solid (yield 98%); <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 8.13-8.07 (m, 1H), 7.70-7.64 (m, 1H), 7.16-7.12 (m, 1H), 3.78-3.73 (m, 4H), 3.55-3.49 (m, 2H), 3.44-3.36 (m, 2H), 3.19-3.13 (m, 2H), 3.06-3.00 (m, 6H), 2.05-1.95 (m, 2H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 147.88, 137.39, 131.60, 127.81, 122.66, 118.02, 66.23, 54.45, 51.02, 49.30, 48.27, 46.16, 29.46; MS (posES-FIA) 25 m/z = 372 (M+H<sup>+</sup>). To a solution of 1-[4-(4-morpholinylsulfonyl)-2-nitrophenyl]-1,4-diazepane (0.445 g, 1.20 mmol) in 30 mL of a 4:1 EtOH:THF solvent system was added Raney-Ni (100 mg suspension in EtOH) followed by hydrazine monohydrate (300 mg, 6.00 mmol). The mixture was stirred vigorously for 4 h and then filtered through celite that was pretreated with water. The filtrate was concentrated, and then re-dissolved in CH<sub>3</sub>CN, 30 concentrated again and finally toluene was added and the mixture concentrated once more to give a brown solid. The crude product was purified by column chromatography (SiO<sub>2</sub>,

CHCl<sub>3</sub>/MeOH/NH<sub>3</sub> 9:1:0.4%) to give 0.365g (yield 89%) of the pure product as a solid. The free base was converted to its HCl salt; <sup>1</sup>H NMR (DMSO-d6) δ 9.34 (s, 2H), 7.23-7.16 (m, 2H), 7.04-6.98 (m, 1H), 3.65-3.60 (m, 4H), 3.35-3.20 (m, 6H), 3.11-3.04 (m, 2H), 2.86-2.80 (m, 4H), 2.09-1.99 (m, 2); MS (posESI) m/z = 341 (M+H<sup>+</sup>).

5

### INTERMEDIATE 17

#### **4-Chloro-N-(2-methoxy-phenyl)-3-nitrobenzenesulfonamide (Scheme 5, Method 5)**

4-Chloro-3-nitrobenzenesulfonamide (1.73 g, 6.78 mmol) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (7.0 mL). *o*-Anisidine (1.00 g, 8.13 mmol) was added dropwise at room temperature, followed by a slow addition of pyridine (2.0 mL). After 16 h of continued stirring, the reaction mixture was diluted with EtOAc (50 mL) and washed with 1 M HCl (3 x 50 mL). The organic phase was dried (MgSO<sub>4</sub>) filtered and evaporated to a brown solid, upon which re-crystallization from ethanol/water gave 2.22 g (95%) of the product as white crystals. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 8.20 (s, 1H), 7.80 (dd, 1H), 7.56 (d, 1H), 7.53 (d, 1H), 7.13 (t, 1H), 6.96 (t, 1H), 6.76 (d, 1H), 3.66 (s, 3H). The sulfonamide proton was not observed.

### INTERMEDIATE 18

#### **20 4-Chloro-3-nitro-N-phenyl-benzenesulfonamide (Scheme 5, Method 5)**

Two portions of 4-Chloro-3-nitrobenzenesulfonamide (1.73 g, 6.78 mmol) were dissolved in CH<sub>2</sub>Cl<sub>2</sub> (7.0 mL) in reaction flasks. Aniline (757 mg, 8.13 mmol) was added drop-wise at room temperature, followed by slow additions of pyridine (2.0 mL). After 16 h of continued stirring, the reaction mixtures were diluted with ethyl acetate (50 mL) and washed with 1 M HCl (3x50 mL). The organic phases were dried (MgSO<sub>4</sub>) and evaporated to brown solids, which upon re-crystallization from ethanol/water gave off-white solid of the product 2.04 g (96%): <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ 8.24 (d, 1H), 7.80 (dd, 1H), 7.61 (d, 1H), 7.30 (t, 2H), 7.20 (t, 1H), 7.09 (d, 2H), 6.79 (bs, 1H); MS (Cl) 310.8 (M - H)<sup>+</sup>; Purity (HPLC, Hichrom 200x4.6 mm I.D.) >98%.

30

**General procedure for reactions between 4-Chloro-3-nitro-N-aryl-benzenesulfonamides and amines ( $R^5$ ) (Scheme 5, Method 5)**

Solutions of Intermediate 17 (343 mg, 1.00 mmol) and Intermediate 12 (313 mg, 1.00 mmol) in CH<sub>3</sub>CN (5 mL) were treated with K<sub>2</sub>CO<sub>3</sub> (276 mg, 2.00 mmol) and amines (R<sup>5</sup>) (1.30 mmol) and heated to 80°C for 16 h. The reaction mixtures were diluted with ethyl acetate (50 mL), washed with saturated Na<sub>2</sub>CO<sub>3</sub> (3x50 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated to products that could be used for the next step without purification.

**INTERMEDIATE 19**

10

**N-(2-Methoxyphenyl)-4-(3-methyl-piperazin-1-yl)-3-nitrobenzenesulfonamide (Scheme 5, Method 5)**

A solution of Intermediate 17 (343 mg, 1.00 mmol) and K<sub>2</sub>CO<sub>3</sub> (276 mg, 2.00 mmol) in CH<sub>3</sub>CN (5 mL) was treated with 2-methylpiperazine (130 mg, 1.30 mmol). After 16 h of stirring at 80°C, the reaction mixture was diluted with EtOAc (50 mL) and washed with saturated Na<sub>2</sub>CO<sub>3</sub> (aq) (3x50 mL). The organic phases were dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated to give 398 mg of a yellow foam of the title compound (98%). <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 8.16 (d, 1H), 7.70 (dd, 1H), 7.50 (d, 1H), 7.06 (t, 1H), 6.97 (d, 1H), 6.91 (t, 1H), 6.75 (d, 1H), 3.69 (s, 3H), 2.92-3.17 (m, 6H), 2.61 (t, 1H), 1.05 (d, 3H). The sulfonamide and amine protons were not observed.

**INTERMEDIATE 20**

25

**4-(Hexahydro-pyrrolo[1,2-a]pyrazin-2-yl)-N-(2-methoxyphenyl)-3-nitro-benzenesulfonamide (Scheme 5, Method 5)**

A solution of Intermediate 17 (343 mg, 1.00 mmol) and K<sub>2</sub>CO<sub>3</sub> (276 mg, 2.00 mmol) in CH<sub>3</sub>CN (5 mL) was treated with octahydropyrrolo[1,2-a]pyrazine (164 mg, 1.30 mmol). After 16 h of stirring at 80 °C, the reaction mixture was diluted with EtOAc (50 mL) and washed with saturated Na<sub>2</sub>CO<sub>3</sub> (3 x 50 mL). The organic phases were dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated to give 407 mg a yellow foam of the title compound (94%). <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 8.16 (s, 1H), 7.70 (dd, 1H), 7.50 (d, 1H), 7.06 (t, 1H), 7.00 (d, 1H), 6.91 (t, 1H), 6.75 (d, 1H),

3.69 (s, 3H), 3.02-3.33 (m, 5H), 2.80 (t, 1H), 2.39 (t, 1H), 2.18-2.22 (m, 2H), 1.76-1.85 (m, 3H), 1.37-1.40 (m, 1H). The sulfonamide and amine protons were not observed.

#### INTERMEDIATE 21

5

##### **3-Nitro-N-phenyl-4-piperazin-1-yl-benzenesulfonamide (Scheme 5, Method 5)**

The compound was prepared from Intermediate 18 and piperazine to give 362 mg bright orange solid (100%):  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  8.16 (d, 1H), 7.68 (d, 1H), 7.27 (t, 2H), 7.15 (t, 1H), 7.08 (d, 2H), 7.01 (d, 1H), 3.13 (t, 4H), 2.98 (t, 4H); MS (CI) 362.8 ( $M + \text{H}^+$ )<sup>+</sup> 361.2 ( $M - \text{H}^-$ ); Purity (HPLC, Hichrom 200x4.6 mm I.D.) 91%.

#### INTERMEDIATE 22

15        **4-(3-Methyl-piperazin-1-yl)-3-nitro-N-phenyl-benzenesulfonamide (Scheme 5, Method 5)**

The compound was prepared from Intermediate 18 and 1-methylpiperazine to give 373 mg orange-brown solid (99%):  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  8.17 (s, 1H), 7.68 (d, 1H), 7.27 (t, 2H), 7.15 (t, 1H), 7.08 (d, 2H), 7.00 (d, 1H), 3.14-3.22 (m, 2H), 2.97-3.06 (m, 4H), 2.64 (dd, 1H), 1.06 (d, 3H); MS (CI) 391.0 ( $M + \text{H}^+$ )<sup>+</sup> 389.4 ( $M - \text{H}^-$ ); Purity (HPLC, Hichrom 200x4.6 mm I.D.) >95%.

#### INTERMEDIATE 23

##### **4-(4-Ethyl-piperazin-1-yl)-3-nitro-N-phenyl-benzenesulfonamide (Scheme 5, Method 5)**

25        The compound was prepared from Intermediate 18 and 1-ethylpiperazine to give 386 mg orange foam (99%):  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  8.19 (s, 1H), 7.72 (dd, 1H), 7.31 (t, 2H), 7.18 (t, 1H), 7.11 (d, 2H), 7.04 (d, 1H), 3.22 (bs, 4H), 2.60 (bs, 4H), 2.50 (q, 2H), 1.13 (t, 3H); MS (CI) 377.0 ( $M + \text{H}^+$ )<sup>+</sup> 375.4 ( $M - \text{H}^-$ ); Purity (HPLC, Hichrom 200x4.6 mm I.D.) >98%.

30

#### INTERMEDIATE 24

**4-(Hexahydro-pyrrolo[1,2-a]pyrazin-2-yl)-3-nitro-N-phenyl-benzenesulfonamide  
(Scheme 5, Method 5)**

The compound was prepared from Intermediate 18 and hexahydro-pyrrolo[1,2-a]2-pyrazine 372 mg orange foam (92%):  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  8.16 (s, 1H), 7.67 (d, 1H), 7.27 (t, 2H), 7.14 (t, 1H), 7.08 (d, 2H), 7.03 (d, 1H), 3.02-3.35 (m, 5H), 2.83 (dd, 1H), 2.41 (t, 1H), 2.18-2.25 (m, 2H), 1.72-1.85 (m, 3H), 1.32-1.43 (m, 1H); MS (CI) 403.2 ( $M + \text{H}^+$ )<sup>+</sup> 401.0 ( $M - \text{H}^-$ ) ; Purity (HPLC, Hichrom 200x4.6 mm I.D.) >95%.

10 INTERMEDIATE 25

**4-(5-Methyl-2,5-diaza-bicyclo[2.2.1]hept-2-yl)-3-nitro-N-phenyl-benzenesulfonamide  
(Scheme 5, Method 5)**

The compound was prepared from Intermediate 18 and 5-methyl-2,5-diaza-bicyclo[2.2.1]2-heptane to give 374 mg yellow solid (96%):  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  8.12 (d, 1H), 7.58 (d, 1H), 7.26 (t, 2H), 7.13 (t, 1H), 7.07 (d, 2H), 6.76 (d, 1H), 4.24 (bs, 1H), 3.46-3.49 (m, 2H), 2.88 (d, 1H), 2.80 (t, 2H); 2.33 (s, 3H), 1.89 (d, 1H), 1.53 (bs, 1H); MS (CI) 389.0 ( $M + \text{H}^+$ )<sup>+</sup> 387.0 ( $M - \text{H}^-$ ) ; Purity (HPLC, Hichrom 200x4.6 mm I.D.) >95%.

20 INTERMEDIATE 26

**4-(trans-2,5-Dimethyl-piperazin-1-yl)-N-(2-methoxyphenyl)-3-nitro-benzenesulfonamide (Scheme 5, Method 5)**

The compound was prepared from Intermediate 17 and 4-(trans-2,5-dimethyl-piperazine to give 409 mg of yellow solid resulted (97%):  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  7.94 (d, 1H), 7.76 (dd, 1H), 7.50 (dd, 1H), 7.28 (d, 1H), 7.10 (t, 1H), 6.93 (t, 1H), 6.73 (d, 1H), 2.93-3.08 (m, 4H), 2.60 (dd, 1H), 2.31 (dd, 1H), 1.01 (d, 3H), 0.73 (d, 3H); MS (CI) 420.8 ( $M + \text{H}^+$ )<sup>+</sup> 418.8 ( $M - \text{H}^-$ ) ; Purity (HPLC, Hichrom 200x4.6 mm I.D.) >95%.

30 General procedure for reduction of the amino groups (Scheme 5, Method 5)

Solutions of the nitro compounds (0.25 mmol) in THF (10 mL) and methanol (2 mL) were treated with Raney-Ni (100 mg) and hydrazine monohydrate (120  $\mu$ L, 2.5 mmol). After stirring at room temperature for 7 h, the suspensions were filtered through celite and washed with ethyl acetate and ethanol. Evaporation with HCl in ether gave the products. Some of the 5 products were without impurities, others had to be purified with HPLC ((YMC combiprep ODS-AQ, 50x20mm I.D.).

#### EXAMPLE 101

10 **3-Amino-N-(2-methoxyphenyl)-4-(3-methyl-piperazin-1-yl)-benzenesulfonamide  
(Scheme 5, Method 5)**

The compound was prepared from *N*-(2-methoxyphenyl)-4-(3-methylpiperazin-1-yl)-3-nitro-benzenesulfonamide to give 90 mg of the title compound (96%).  $^1$ H NMR (CDCl<sub>3</sub>)  $\delta$  7.44 (d, 1H), 7.11 (d, 1H), 7.10 (d, 1H), 6.97 (t, 1H), 6.85 (d, 1H), 6.84 (t, 1H), 6.72 (d, 1H), 3.97 (bs, 2H), 3.62 (s, 3H), 2.91-3.06 (m, 5H), 2.56 (t, 1H), 2.23 (t, 1H), 1.41 (s, 1H), 1.05 (d, 3H). The sulfonamide protons were not observed.  $^{13}$ C NMR (CDCl<sub>3</sub>)  $\delta$  149.4, 143.1, 141.4, 134.6, 125.4, 124.4, 121.0, 120.4, 119.2, 117.7, 113.2, 110.5, 55.6, 51.1, 50.8, 46.3, 30.3, 19.6. MS (CI neg) 375 (M-H<sup>+</sup>), (CI pos) 377 (M+H<sup>+</sup>).

20 EXAMPLE 102

**3-Amino-4-(hexahydro-pyrrolo[1,2-a]pyrazin-2-yl)-N-(2-methoxyphenyl)-benzenesulfonamide (Scheme 5, Method 5)**

The compound was prepared from 4-(hexahydro-pyrrolo[1,2-a]pyrazin-2-yl)-*N*-(2-methoxyphenyl)-3-nitrobenzenesulfonamide to give 97 mg of the title compound (96%).  $^1$ H NMR (CDCl<sub>3</sub>)  $\delta$  7.44 (d, 1H), 7.12 (d, 1H), 7.11 (d, 1H), 6.97 (t, 1H), 6.90 (d, 1H), 6.84 (t, 1H), 6.72 (d, 1H), 3.96 (bs, 2H), 3.62 (s, 3H), 3.19 (d, 1H), 3.09 (app t, 3H), 2.76 (t, 1H), 2.45 (t, 1H), 2.31-2.38 (m, 1H), 2.10-2.21 (m, 2H), 1.72-1.87 (m, 3H), 1.21 (t, 1H). The sulfonamide protons were not observed.  $^{13}$ C NMR (CDCl<sub>3</sub>)  $\delta$  149.4, 143.1, 141.4, 134.4, 125.4, 124.7, 121.0, 120.5, 119.5, 117.7, 113.2, 110.5, 55.6, 55.0, 53.3, 52.0, 49.7, 30.3, 27.3, 21.2. MS (CI neg) 401 (M-H<sup>+</sup>).

## EXAMPLE 103

**3-Amino-N-phenyl-4-piperazin-1-yl-benzenesulfonamide hydrochloride (Scheme 5,****5 Method 5)**

The compound was prepared from N-phenyl-4-piperazin-1-yl-3-nitro benzenesulfonamide to give 15 mg yellow solid (18%):  $^1\text{H}$  NMR (MeOD, 400 MHz)  $\delta$  7.57-7.61 (m, 2H), 7.40 (d, 1H), 7.23 (t, 2H), 7.13 (d, 2H), 7.07 (t, 1H), 3.45 (t, 4H), 3.20 (t, 4H); MS (CI) 333.0 ( $M + H$ ) $^+$  331.4 ( $M - H$ ) $^-$ ; Purity (HPLC, Hichrom 200x4.6 mm I.D.) 96%.

10

## EXAMPLE 104

**3-Amino-4-(3-methyl-piperazin-1-yl)-N-phenyl-benzenesulfonamide hydrochloride (Scheme 5, Method 5)**

15 The compound was prepared from 4-(3-methyl-piperazin-1-yl)-N-3-nitrophenyl-benzenesulfonamide to give 33 mg white solid (35%):  $^1\text{H}$  NMR (MeOD, 400 MHz)  $\delta$  7.57-7.62 (m, 2H), 7.35-7.41 (m, 1H), 7.12 (t, 2H), 7.02 (d, 2H), 6.97 (t, 1H), 3.53-3.58 (m, 1H), 3.31-3.40 (m, 2H), 3.16 (t, 2H), 2.99-3.05 (m, 1H), 2.79 (t, 1H), 1.27 (d, 3H); MS (CI) 346.8 ( $M + H$ ) $^+$  345.4 ( $M - H$ ) $^-$ ; Purity (HPLC, Hichrom 200x4.6 mm I.D.) 100%.

20

## EXAMPLE 105

**3-Amino-4-(4-ethyl-piperazin-1-yl)-N-phenyl-benzenesulfonamide hydrochloride (Scheme 5, Method 5)**

25 The compound was prepared from 3-Amino-4-(4-ethyl-piperazin-1-yl)-N-phenyl-benzenesulfonamide to give 32 mg white solid (33%):  $^1\text{H}$  NMR (MeOD, 400 MHz)  $\delta$  7.52-7.57 (m, 2H), 7.36 (d, 1H), 7.12 (t, 2H), 7.01 (d, 2H), 6.96 (t, 1H), 3.56 (d, 2H), 3.26 (t, 2H), 3.17-3.23 (m, 4H), 3.09 (t, 2H), 1.31 (t, 3H); MS (CI) 361.0 ( $M + H$ ) $^+$  359.4 ( $M - H$ ) $^-$ ; Purity (HPLC, Hichrom 200x4.6 mm I.D.) 96%.

30

## EXAMPLE 106

**3-Amino-4-(hexahydro-pyrrolo[1,2-a]pyrazin-2-yl)-N-phenyl-benzenesulfonamide hydrochloride (Scheme 5, Method 5)**

5        The compound was prepared from 4-(hexahydro-pyrrolo[1,2-a]pyrazin-2-yl)-N-phenyl-3-nitro-benzenesulfonamide to give 50 mg white solid (49%):  $^1\text{H}$  NMR (MeOD, 400 MHz)  $\delta$  7.63-7.69 (m, 2H), 7.47-7.52 (m, 1H), 7.23 (t, 2H), 7.13 (d, 2H), 7.08 (t, 1H), 3.08-3.78 (m, 8H), 2.12-2.35 (m, 4H), 1.79-1.88 (m, 1H); MS (CI) 372.8 ( $M + H$ ) $^+$  371.4 ( $M - H$ ) $^-$ ; Purity (HPLC, Hichrom 200x4.6 mm I.D.) 100%.

10

## EXAMPLE 107

**3-Amino-4-(5-methyl-2,5-diaza-bicyclo[2.2.1]hept-2-yl)-N-phenyl-benzenesulfonamide hydrochloride (Scheme 5, Method 5)**

15        The compound was prepared from 4-(5-methyl-2,5-diaza-bicyclo[2.2.1]hept-2-yl)-N-phenyl-3-nitrobenzenesulfonamide to give 40 mg red solid (40%):  $^1\text{H}$  NMR (MeOD, 400 MHz, major conformer at 300 K)  $\delta$  7.49-7.56 (m, 2H), 7.09-7.15 (m, 3H), 6.99-7.05 (m, 2H), 6.95 (t, 1H), 4.39 (bs, 1H), 4.30 (bs, 1H), 3.89 (d, 1H), 3.56 (bs, 2H), 3.09 (d, 1H), 2.88 (s, 3H), 2.34 (d, 1H), 2.20 (d, 1H); MS (CI) 359.0 ( $M + H$ ) $^+$  357.4 ( $M - H$ ) $^-$ ; Purity (HPLC, Hichrom 200x4.6 mm I.D.) 93%.

## EXAMPLE 108

25        **3-Amino-4-(trans-2,5-dimethyl-piperazin-1-yl)-N-(2-methoxy-phenyl)-benzenesulfonamide hydrochloride (Scheme 5, Method 5)**

The compound was prepared from 4-(trans-2,5-dimethyl-piperazin-1-yl)-N-(2-methoxy-phenyl)-3-nitrobenzenesulfonamide to give 60 mg white solid (61%):  $^1\text{H}$  NMR (MeOD, 400 MHz)  $\delta$  7.54-7.58 (m, 2H), 7.45 (d, 1H), 7.32 (d, 1H), 7.02 (t, 1H), 6.81 (d, 1H), 6.76 (t, 1H), 3.54-3.57 (m, 1H), 3.47 (s, 3H), 3.37 (d, 1H), 3.30-3.34 (m, 1H), 3.01 (t, 2H), 2.71 (t, 1H), 1.23 (d, 3H), 0.77 (d, 3H); MS (CI) 390.8 ( $M + H$ ) $^+$  389.4 ( $M - H$ ) $^-$ ; Purity (HPLC, Hichrom 200x4.6 mm I.D.) 96%.

## EXAMPLE 112

**4-[4-(3,4-Dihydro-2H-quinoline-1-sulfonyl)-2-amino-phenyl]-[1,4]diazepane**5 **ditrifluoroacetic acid (Scheme 5, Method 5)**

The compound was prepared from 1,2,3,4-tetrahydro-quinoline 4-chloro-3-nitro-benzenesulfonyl chloride and [1,4]diazepane-1-carboxylic acid tert-butyl ester (430 µl, 2.2 mmol) to give (63%) as a solid.  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  7.69-7.62 (m, 1H), 7.16-6.98 (m, 5H), 6.94-6.89 (m, 1H), 3.78-3.71 (m, 2H), 3.46-3.27 (m, 6H), 3.13-3.06 (m, 2H), 2.48-2.40 (m, 10 2H), 2.16-2.05 (m, 2H), 1.69-1.58 (m, 2H); MS  $m/z$  (M+1) 387.

## EXAMPLE 109

**2-(3-Amino-4-[1,4]diazepan-1-yl-benzenesulfonyl)-benzamide diacetic acid (Scheme 5,**15 **Method 5)**

The compound was prepared from 2-amino-benzamide, 4-chloro-3-nitro-benzenesulfonyl chloride and 1,4]diazepane-1-carboxylic acid tert-butyl to give (1%) as an oil:  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  7.68-7.57 (m, 2H), 7.43-7.36 (m, 1H), 7.17-7.15 (m, 1H), 7.10-7.02 (m, 3H), 3.44-3.25 (m, 6H), 3.12-3.05 (m, 2H), 2.14-2.02 (m, 2H); MS  $m/z$  (M+1) 390.

20

## EXAMPLE 111

**2-[1,4]Diazepan-1-yl-5-(3,4-dihydro-1H-isoquinoline-2-sulfonyl)-aniline****dihydrochloride (Scheme 5, Method 5)**

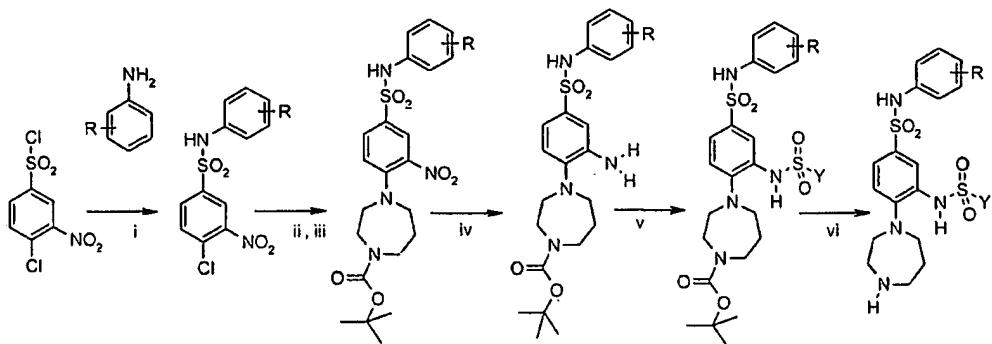
25 The compound was prepared from 1,2,3,4-tetrahydro-isoquinoline, 4-chloro-3-nitro-benzenesulfonyl chloride and 1,4]diazepane-1-carboxylic acid tert-butyl ester to give (93%) as a white solid.  $^1\text{H}$  NMR ( $\text{DMSO}$ )  $\delta$  9.28 (s, 2 H), 7.12 (m, 7 H), 4.12 (s, 2 H), 3.20 (m, 8 H), 3.02 (t,  $J = 5.81$  Hz, 2 H), 2.86 (t,  $J = 6.07$  Hz, 2 H), 2.00 (m, 2 H); MS  $m/z$  387 (M+1).

30 EXAMPLE 110

**4-[4-(3-Fluoro-2-methoxy-phenylsulfamoyl)-2-amino-phenyl]-[1,4]diazepane  
ditrifluoroacetic acid (Scheme 5, Method 5)**

The compound was prepared from 3-fluoro-2-methoxyaniline, 4-chloro-3-nitrobenzenesulfonyl chloride and 1,4]diazepane-1-carboxylic acid tert-butyl ester to give (43%)  
5 as a solid.  $^1\text{H}$  NMR (DMSO)  $\delta$  9.70 (s, 1H), 8.79 (br s, 2H), 7.17-6.87 (m, 6H), 3.53 (s, 3H),  
3.32-3.13 (m, 6H), 2.99-2.91 (m, 2H), 2.01-1.89 (m, 2H); MS  $m/z$  (M+1) 395.

**Scheme 6, Method 6**



10

**Legend to Scheme 2:**

i: Py,  $\text{CH}_2\text{Cl}_2$ ; ii:  $\text{K}_2\text{CO}_3$ ,  $\text{CH}_3\text{CN}$ , diamine (i. e. homopiperazine); iii:  $(\text{BOC})_2\text{O}$ , THF, NaOH; iv: Raney-Ni, Hydrazine monohydrate, THF/EtOH; v: sulfonylchloride ( $\text{Y}-\text{SO}_2-\text{Cl}$ ), Py,  $\text{Et}_3\text{N}$ ,  $\text{CH}_2\text{Cl}_2$ ; vi: HCl ether/MeOH

15

**INTERMEDIATE 27**

**tert-Butyl- 4-[4-(anilinosulfonyl)-2-nitrophenyl]-1,4-diazepane-1-carboxylate (Scheme 6, Method 6)**

20 Di-*tert*-butyl dicarbonate (0.921 g, 4.22 mmol) in THF (20.0 mL) was added to a solution of 4-(1,4-diazepan-1-yl)-3-nitro-N-phenylbenzenesulfonamide (0.530 g, 1.40 mmol) and NaOH (0.140 g, 3.50 mmol) dissolved in THF:water (30 mL, 1:1). The solution was stirred at room temperature for 3 h. The mixture was neutralized with 5 N HCl and then the THF was removed under vacuum. The aqueous phase was extracted with  $\text{CHCl}_3$  (2 x 50 mL)

and the combined organic layers were dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated. Purification via flash column chromatography ( $\text{SiO}_2$ , using  $\text{CHCl}_3/\text{MeOH}/9.75:0.25$ ) gave a solid, which was triturated with  $\text{EtOAc}/\text{pentane}$  to give 0.605 g (90%) of the pure product.  $^1\text{H}$  NMR (DMSO-*d*6)  $\delta$  9.84 (br s, 1H), 8.01-7.98 (m, 1H), 7.70-7.65 (m, 1H), 7.32-7.28 (m, 1H), 7.26-7.20 (m, 2H), 7.13-7.08 (m, 2H), 7.07-7.02 (m, 1H), 3.61-3.48 (m, 4H), 3.39-3.33 (m, 2H), 3.23-3.15 (m, 2H), 1.85-1.76 (m, 2H), 1.18 (s, 9H); MS (posESI-FIA) m/z = 477 ( $\text{M}+\text{H}^+$ ). *tert*-Butyl-4-[2-nitro-4-(anilinosulfonyl)phenyl]-1,4-diazepane-1-carboxylate was reduced to the final product by treatment with Raney-Ni and hydrazine monohydrate using method C to yield 0.477 g (91%) of the free base;  $^1\text{H}$  NMR (DMSO-*d*6)  $\delta$  9.81 (s, 1H), 7.24-7.18 (m, 2H), 7.13-7.08 (m, 3H), 7.02-6.92 (m, 3H), 4.99 (m, 2H), 3.53-3.45 (m, 4H), 3.02-2.94 (m, 4H), 1.86-1.79 (m, 2H), 1.42 (9H); MS (posESI-FIA) m/z = 447 ( $\text{M}+\text{H}^+$ ).

#### EXAMPLE 97

15 **4-(1,4-Diazepan-1-yl)-N-phenyl-3-[(methylsulfonyl)amino]benzenesulfonamide hydrochloride (Scheme 6, Method 6)**

A mixture of *tert*-butyl 4-[2-amino-4-(anilinosulfonyl)phenyl]-1,4-diazepane-1-carboxylate (176 mg, 0.39 mmol), methylsulfonyl chloride (0.040 mL, 0.47 mmol) and pyridine (0.285 mL, 3.51 mmol) in  $\text{CH}_2\text{Cl}_2$  (5 mL) was stirred at room temperature 20 overnight. The reaction mixture was quenched with  $\text{NaHCO}_3$  aq (3 x 30 mL). The organic phase was separated, dried ( $\text{MgSO}_4$ ) and filtered. The volatiles were evaporated followed by purification of the oily residue by chromatography ( $\text{SiO}_2$ , hexane/ $\text{EtOAc}$  4:1) to give 110 mg of *tert*-butyl 4-{4-(anilinosulfonyl)-2-[(methylsulfonyl)amino]phenyl}-1,4-diazepane-1-carboxylate (yield 58 %).

25  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.90-7.85 (m, 1H), 7.50-7.43 (m, 1H), 7.30-7.24 (m, 2H), 7.20-7.08 (m, 4H), 6.84-6.79 (m, 1H), 3.65-3.51 (m, 4H), 3.12-3.06 (m, 1H), 3.04-2.96 (m, 6H), 2.04-1.91 (m, 2H), 1.49 (s, 3H); MS (posEI-DIP) m/z = 524 ( $\text{M}+\text{H}^+$ ). *tert*-Butyl 4-{4-(anilinosulfonyl)-2-[(methylsulfonyl)amino]phenyl}-1,4-diazepane-1-carboxylate (0.077 g, 0.147 mmol) was dissolved in  $\text{MeOH}$ , and ether saturated with  $\text{HCl}$  gas 30 was added. The mixture was stirred at room temperature for 4 h and then concentrated. The crude solid was dissolved in a small amount of  $\text{MeOH}$ , and ether was added. The precipitate

was collected and dried to give 30 mg of the pure product as the HCl salt (yield 48%):  $^1\text{H}$  NMR (DMSO-d6)  $\delta$  7.72-7.70 (m, 1H), 7.46-7.42 (m, 1H), 7.25-7.20 (m, 3H), 7.14-7.09 (m, 2H), 7.03-6.99 (m, 1H), 3.45-3.15 (m, partly obscured by solvent signal, HDO, 6H), 2.96 (s, 3H), 2.02-1.95 (m, 2H); MS (posES-FIA) m/z = 425 ( $\text{M}+\text{H}^+$ ).

5

#### EXAMPLE 96

##### **4-(1,4-Diazepan-1-yl)-N-phenyl-3-[(phenylsulfonyl)amino]benzenesulfonamide hydrochloride (Scheme 6, Method 6)**

To a solution of tert-butyl 4-[2-amino-4-(anilinosulfonyl)phenyl]-1,4-diazepane-1-carboxylate (0.268 g, 0.599 mmol), pyridine (338  $\mu\text{L}$ , 4.19 mmol) and  $\text{Et}_3\text{N}$  (337  $\mu\text{L}$ , 2.40 mmol), in  $\text{CH}_2\text{Cl}_2$  (8.0 mL) was added benzenesulfonyl chloride (153  $\mu\text{L}$ , 1.20 mmol) in  $\text{CH}_2\text{Cl}_2$  (2 mL). The mixture was stirred at room temperature for 16 h. The reaction mixture was washed with saturated aqueous  $\text{NaHCO}_3$ , dried with  $\text{Na}_2\text{SO}_4$ , filtered and concentrated.

The crude material was dissolved in EtOH (5 mL) and KOH (0.134 g, 4.0 equiv.) was added. The reaction was stirred at room temperature for 2 days. Water (5 mL) was added to the reaction mixture and most of the EtOH was evaporated under vacuum. The water phase was extracted with  $\text{CH}_2\text{Cl}_2$  (3x20 mL). The combined organic phases were dried with  $\text{Na}_2\text{SO}_4$ , filtered and concentrated. The crude boc-protected material was dissolved in MeOH, and ether saturated with HCl gas was added. The mixture was stirred for 16 h and then concentrated to give 0.543 g of the crude product, which was purified by reversed phase preparative HPLC to give 0.153 g of the pure product as the acetic acid salt which was converted to the HCl-salt:  $^1\text{H}$  NMR (DMSO-d6)  $\delta$  10.25 (s, 1H), 9.09 (br s, 2H), 7.68-7.58 (m, 4H), 7.54-7.48 (m, 2H), 7.46-7.42 (m, 1H), 7.23-7.16 (m, 3H), 7.05-6.28 (m, 3H), 3.35-3.15 (m, partly obscured by solvent signal HDO, 6H), 2.81-2.75 (m, 2H), 1.92-1.85 (m, 2H); MS (posES-FIA) m/z = 487 ( $\text{M}+\text{H}^+$ ).

#### INTERMEDIATE 28

**N-Naphthalen-1-yl-3-nitro-4-piperazin-1-yl-benzenesulfonamide, hydrochloride**

4-Chloro-3-nitrobenzenesulphonyl chloride (0.992 g, 3.87 mmol) was added to a solution of naphthalen-1-ylamine (0.665 g, 4.64 mmol) and pyridine (3.1 mL, 38.7 mmol) dissolved in DCM (5 mL). The solution was stirred at room temperature for 2 days and the volatiles were evaporated. The crude mixture was dissolved in EtOAc and the organic phase was washed with 1 N HCl, dried with MgSO<sub>4</sub>, filtered and concentrated to give 1.1 g of naphthalen-1-yl-3-nitro-4-chloro-benzenesulphonamide. Naphthalen-1-yl-3-nitro-4-chlorobenzenesulphonamide was dissolved in CH<sub>3</sub>CN (10 mL) and piperazine (0.683 g, 7.93 mmol) was added. The mixture was stirred at 65 °C for 16 hours. The mixture was concentrated and the crude product was purified by flash chromatography on silica using DCM→DCM/MeOH (10%) + aqueous NH<sub>3</sub> (0.4 as eluent to give 0.531 g of the free base which was converted to its HCl-salt.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ 10.36 (brs, 1H), 9.33 (brs, 2H), 8.12 (D, J = 2.1 Hz, 1H), 8.05-7.99 (m, 1H), 7.94-7.88 (m, 1H), 7.85-7.72 (m, 2H), 7.55-7.38 (m, 4H), 7.22-7.16 (m, 1H), 3.40-3.30 (m, obscured by solvent signal, 4H), 3.24-3.12 (m, 4H); MS (posES-FIA) m/z = 413 (M+H).

**EXAMPLE 113****20 3-Amino-2-chloro-N-naphthalen-1-yl-4-piperazin-1-yl-benzenesulfonamide, hydrochloride**

To a solution of N-naphthalen-1-yl-3-nitro-4-piperazin-1-yl-benzenesulfonamide (0.4602 g, 11.2 mmol) in 40 mL of a 4:1 EtOH:THF solvent system was added Raney-Ni (~ 1.0 mL suspension in EtOH) followed by hydrazine mono-hydrate (2.80 g, 56.0 mmol). The mixture was stirred vigorously for 3 hours and then filtered through celite. The filtrate was concentrated and the crude product was triturated with MeOH/ether. The product was converted to its HCl-salt. Yield (90%) as the free base. An aliquot was purified by preparative LC/MS.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ 9.20-8.90 (brs 2H), 8.25-8.21 (m, 1H), 7.90-7.86 (m, 1H), 7.74 (d, J = 8.48 Hz, 1H), 7.52-7.46 (m, 2H), 7.39-7.35 (m, 1H), 7.24-7.21 (m, 1H), 7.10 (d, J = 8.48

Hz, 1H), 6.91 (m, d,  $J = 8.48$  Hz, 1H), 3.32-3.25 (m,, obscured by solvent signal, 4H), 3.03-2.98 (m, 4H); MS (posES-FIA) m/z = 383.

## BIOLOGICAL TESTS

5

The ability of a compound according to the invention to bind a 5-HT<sub>6</sub> receptor, and to be pharmaceutically useful, can be determined using *in vivo* and *in vitro* assays known in the art.

### (a) 5-HT<sub>6</sub> Intrinsic Activity Assay

10 Antagonists to the 5-HT<sub>6</sub> receptor were characterized by measuring inhibition of 5-HT induced increase in cAMP in HEK 293 cells expressing the human 5-HT<sub>6</sub> receptor (see Boess et al. (1997) Neuropharmacology 36: 713-720). Briefly, HEK293/5-HT<sub>6</sub> cells were seeded in polylysine coated 96-well plates at a density of 25,000 / well and grown in DMEM (Dulbecco's Modified Eagle Medium) (without phenol-red) containing 5% dialyzed Foetal  
15 Bovine Serum for 48 h at 37°C in a 5% CO<sub>2</sub> incubator. The medium was then aspirated and replaced by 0.1 ml assay medium (Hanks Balance Salt Solution containing 20 mM HEPES, 1.5 mM isobutylmethylxanthine and 1 mg/ml bovine serum albumin). After addition of test substances, 50 µl dissolved in assay medium, the cells were incubated for 10 min at 37°C in a 5% CO<sub>2</sub> incubator. The medium was again aspirated and the cAMP content was determined  
20 using a radioactive cAMP kit (Amersham Pharmacia Biotech, BIOTRAK RPA559). The potency of antagonists was quantified by determining the concentration that caused 50% inhibition of 5-HT (at [5-HT]= 8 times EC<sub>50</sub>) evoked increase in cAMP, using the formula K<sub>i,eff</sub>=IC<sub>50</sub>/(1+[5HT]/EC<sub>50</sub>).

25 The compounds in accordance with the invention have a selective affinity to 5-HT<sub>6</sub> receptors with K<sub>i</sub> values between 1 nM and 5 µM and they antagonized the 5-HT induced increase of cAMP. There is correlation between the K<sub>i</sub> binding and the K<sub>i,efficacy</sub>. Moreover, the compounds show good selectivity (>100 fold) against 5-HT<sub>2a</sub>, 5-HT<sub>2b</sub>, 5-HT<sub>2c</sub>, 5-HT<sub>1a</sub>, 5-HT<sub>1b</sub>.

30

### (b) *In vivo* assay of reduction of food intake

For a review on serotonin and food intake, see Blundell, J.E. and Halford, J.C.G. (1998) Serotonin and Appetite Regulation. Implications for the Pharmacological Treatment of Obesity. CNS Drugs 9:473-495.

5

Obese (ob/ob) mouse is selected as the primary animal model for screening as this mutant mouse consumes high amounts of food resulting in a high signal to noise ratio. To further substantiate and compare efficacy data, the effect of the compounds on food consumption is also studied in wild type (C57BL/6J) mice. The amount of food consumed 10 during 15 hours of infusion of compounds is recorded.

Male mice (obese C57BL/6JBom-Lep<sup>ob</sup> and lean wild-type C57B1/6JBom; Bomholtsgaard, Denmark) 8-9 weeks with an average body weight of 50 g (obese) and 25 g (lean) are used in all the studies. The animals are housed singly in cages at 23±1°C, 40-60 % 15 humidity and have free access to water and standard laboratory chow. The 12/12-h light/dark cycle is set to lights off at 5 p.m. The animals are conditioned for at least one week before start of study.

The test compounds are dissolved in solvents suitable for each specific compound 20 such as cyclodextrin, cyclodextrin/methane sulfonic acid, polyethylene glycol/methane sulfonic acid, saline. Fresh solutions are made for each study. Doses of 30, 50 and 100 mg kg<sup>-1</sup>day<sup>-1</sup> are used. The purity of the test compounds is of analytical grade.

The animals are weighed at the start of the study and randomized based on body 25 weight. Alzet osmotic minipumps (Model 2001D; infusion rate 8 µl/h) are used and loaded essentially as recommended by the Alzet technical information manual (Alza Scientific Products, 1997; Teeuwes and Yam, 1976). Continuous subcutaneous infusion with 24 hours duration is used. The minipumps are either filled with different concentrations of test compounds dissolved in vehicle or with only vehicle solution and maintained in vehicle pre-warmed to 37°C (approx. 1h). The minipumps are implanted subcutaneously in the 30

neck/back region under short acting anesthesia (metofane/enflurane). This surgical procedure lasts approximately 5 min. It takes about 3 h to reach steady state delivery of the compound.

The weight of the food pellets are measured at 5 p.m. and at 8 p. m. for two days  
 5 before (baseline) and one day after the implantation of the osmotic minipumps. The weigh-in is performed with a computer assisted Mettler Toledo PR 5002 balance. Occasional spillage is corrected for. At the end of the study the animals are killed by neck dislocation and trunk blood sampled for later analysis of plasma drug concentrations.

10 The plasma sample proteins are precipitated with methanol, centrifuged and the supernatant is transferred to HPLC vials and injected into the liquid chromatography /mass spectrometric system. The mass spectrometer is set for electrospray positive ion mode and Multiple Reaction Monitoring (MRM with the transition m/z 316  $\Rightarrow$  221).

15 A linear regression analysis of the standards forced through the origin is used to calculate the concentrations of the unknown samples.

Food consumption for 15 hours is measured for the three consecutive days and the percentage of basal level values is derived for each animal from the day before and after  
 20 treatment. The values are expressed as mean  $\pm$  SD and  $\pm$  SEM from eight animals per dose group. Statistical evaluation is performed by Kruskal-Wallis one-way ANOVA using the percent basal values. If statistical significance is reached at the level of p<0.05, Mann-Whitney U-test for statistical comparison between control and treatment groups is performed.

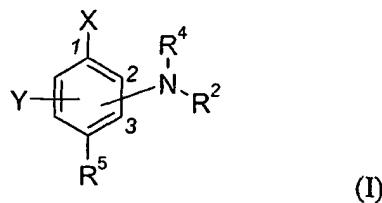
25 The compounds according to the invention show an effect in the range of 50-150 mg/kg.

TABLE VII

EXAMPLE	Dose (mg/Kg)	Reduction of Food Intake (%) <i>po</i> administration
27	50	28
29	100	60

## WHAT IS CLAIMED IS:

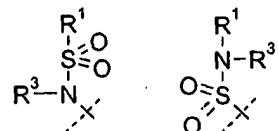
## 1. A compound of the formula (I)



5

or a pharmaceutically acceptable salt thereof, wherein

X is



(la)

(lb)

10      R<sup>1</sup> and R<sup>3</sup> are independently

- (a) H
- (b) C<sub>1-6</sub> alkyl,
- (c) C<sub>1-6</sub> alkoxy,
- (d) straight or branched C<sub>1-6</sub> hydroxyalkyl,
- 15    (e) straight or branched C<sub>1-6</sub> alkylhalides; or
- (f) a group Ar;

Ar is

- (a) phenyl,
- 20    (b) 1-naphthyl,
- (c) 2-naphthyl,
- (d) benzyl,
- (e) cinnamoyl,
- (f) a 5 to 7-membered, partially or completely saturated, heterocyclic ring containing 1 to 4  
25    heteroatoms, selected from oxygen, nitrogen and sulfur, or

(g) a bicyclic ring system consisting of two heterocyclic rings as defined under (f), or a bicyclic ring system consisting of one benzene ring and one heterocyclic ring as defined under (f);

5 alternatively, R<sup>1</sup> and R<sup>3</sup> are linked to form a group (CH<sub>2</sub>)<sub>2</sub>O, (CH<sub>2</sub>)<sub>4</sub>O, or (CH<sub>2</sub>)<sub>3-5</sub> in formula (Ib);

optionally, the group Ar is substituted with

(a) Y, or

10 (b) a 5 to 7-membered, partially or completely saturated, heterocyclic ring each containing 1 to 4 heteroatoms selected from oxygen, nitrogen or sulfur;

Y is

(a) H,

15 (b) halogen,

(c) C<sub>1-6</sub> alkyl,

(d) CF<sub>3</sub>,

(e) hydroxy,

(f) C<sub>1-6</sub> alkoxy,

20 (g) C<sub>1-4</sub> alkenyl;

(h) phenyl;

(i) phenoxy,

(j) benzyloxy,

(k) benzoyl,

25 (l) OCF<sub>3</sub>,

(m) CN,

(n) straight or branched C<sub>1-6</sub> hydroxyalkyl,

(o) straight or branched C<sub>1-6</sub> alkylhalides,

(p) NH<sub>2</sub>,

30 (q) NHR<sup>6</sup>,

(r) NR<sup>6</sup>R<sup>7</sup>,

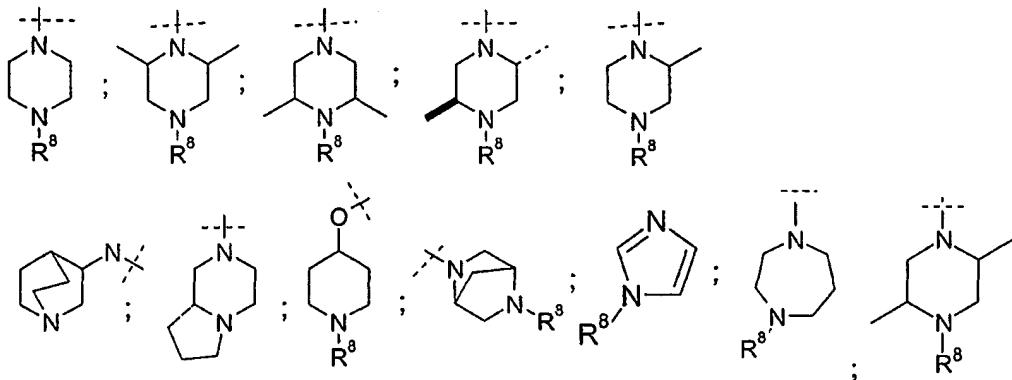
- (s)  $\text{NO}_2$ ,
- (t)  $-\text{CONR}^6\text{R}^7$ ,
- (u)  $\text{NHSO}_2\text{R}^6$ ,
- (v)  $\text{NR}^6\text{COR}^7$ ,
- 5 (x)  $\text{SO}_2\text{NR}^6\text{R}^7$ ,
- (z)  $-\text{C}(=\text{O})\text{R}^6$ ,
- (aa)  $-\text{CO}_2\text{R}^6$ , or
- (ab)  $\text{S}(\text{O})_n\text{R}^6$ , wherein n is 0, 1, 2 or 3;

10  $\text{R}^2$  and  $\text{R}^4$  are independently:

- (a)  $-\text{SO}_2\text{R}^1$ ,
- (b) H,
- (c)  $\text{C}_{1-6}$  alkyl,
- (d)  $\text{C}_{1-3}$  alkenyl,
- 15 (e)  $\text{C}_{1-3}$  alkylaryl,
- (f) Ar as defined above for  $\text{R}^1$ ,
- (g)  $-\text{C}(=\text{O})\text{R}^6$ ,
- (h)  $-\text{C}(\text{O})\text{NR}^6\text{R}^7$ ,
- (i)  $-\text{C}(\text{S})\text{NR}^6\text{R}^7$ ,
- 20 (j)  $-\text{CO}_2\text{R}^6$ ;
- (k)  $-\text{C}(\text{S})\text{R}^6$ ;
- (l) straight or branched  $\text{C}_{1-6}$  hydroxyalkyl, or
- (m) straight or branched  $\text{C}_{1-6}$  alkylhalides;

25 alternatively,  $\text{R}^2$  and  $\text{R}^4$  are linked to form a group  $(\text{CH}_2)_2\text{O}$ ,  $(\text{CH}_2)_4\text{O}$ , or  $(\text{CH}_2)_{3-5}$  in formula (Ia);

$R^5$  is selected from the group consisting of the following chemical groups:



$R^6$  and  $R^7$  are independently

5 (a) H,  
 (b)  $C_{1-6}$  alkyl,  
 (c)  $C_{3-7}$  cycloalkyl, or  
 (d) Ar, as defined above for  $R^1$ ;

10 alternatively,  $R^6$  and  $R^7$  are linked to form a group  $(CH_2)_2O$ ,  $(CH_2)_4O$  or  $(CH_2)_{3-5}$ ;

$R^8$  is

(a) H, or  
 (b)  $C_{1-6}$  alkyl.

15

2. A compound according to claim 1 wherein

$R^1$  is a group Ar;

20 Ar is

(a) phenyl,  
 (b) 1-naphthyl,  
 (c) 2-naphthyl, or

(f) a 5 to 7-membered, partially or completely saturated, heterocyclic ring containing 1 to 4 heteroatoms, selected from oxygen, nitrogen and sulfur;

the group Ar is substituted with Y, wherein Y is

- 5     (a) H,
- (b) halogen,
- (c) C<sub>1-6</sub> alkyl,
- (d) CF<sub>3</sub>,
- (f) C<sub>1-6</sub> alkoxy,
- 10    (g) C<sub>1-4</sub> alkenyl;
- (h) phenyl;
- (l) OCF<sub>3</sub>, or
- (n) straight or branched C<sub>1-6</sub> hydroxyalkyl.

15    3. A compound according to claim 1 or 2, wherein

the group  $\begin{array}{c} \text{R}^4 \\ | \\ -\text{N}-\text{R}^2 \end{array}$  is attached to the phenyl ring in 2-position and 3-position.

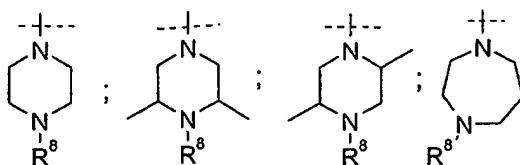
4. A compound according to any one of claims 1 to 3, wherein R<sup>2</sup> is  $-\text{SO}_2\text{R}^1$ .

20

5. A compound according to any one of claims 1 to 4, wherein R<sup>3</sup> and R<sup>4</sup> are independently H, methyl or ethyl.

25

6. A compound according to any one of claims 1 to 5, wherein R<sup>5</sup> is selected from the group consisting of the following chemical groups:



VO

wherein R<sup>8</sup> is H or methyl.

7. A compound according to any one of claims 1 to 6, wherein R<sup>6</sup> and R<sup>7</sup> are independently  
5     (a) H,  
       (b) C<sub>1-6</sub> alkyl,  
       (c) C<sub>3-7</sub> cycloalkyl, or  
       (d) Ar.

10    8. A compound according to claim 1, which is the compound  
         N-[2-{ethyl[(3-fluorophenyl)sulfonyl]amino}-4-(4-methyl-1-piperazinyl)phenyl]-3-  
         fluorobenzenesulfonamide,  
         N-[2-[ethyl(phenylsulfonyl)amino]-4-(4-methyl-1-piperazinyl)phenyl]  
         benzenesulfonamide,  
15    3-fluoro-N-[2-{[(3-fluorophenyl)sulfonyl]amino}-4-(4-methyl-1-piperazinyl)  
         phenyl]benzenesulfonamide,  
         N-{5-(4-methyl-1-piperazinyl)-2-[(8-quinolinylsulfonyl)amino]phenyl}-7-  
         quinolinesulfonamide,  
         N-[2-chloro-4-({4-(4-methyl-1-piperazinyl)-2-[(phenylsulfonyl)amino]anilino}  
20    sulfonyl)phenyl]acetamide,  
         3,4-dimethoxy-N-{4-(4-methyl-1-piperazinyl)-2-[(phenylsulfonyl)amino]phenyl}  
         benzenesulfonamide,  
         3-methoxy-4-methyl-N-{4-(4-methyl-1-piperazinyl)-2-[(phenylsulfonyl)amino]  
phenyl}benzenesulfonamide,  
25    4-methyl-N-{4-(4-methyl-1-piperazinyl)-2-[(methylsulfonyl)amino]phenyl}  
         benzenesulfonamide,  
         3,4-dimethoxy-N-{4-(4-methyl-1-piperazinyl)-2-[(methylsulfonyl)amino]phenyl}  
         benzenesulfonamide,  
         3-cyano-N-{4-(4-methyl-1-piperazinyl)-2-[(methylsulfonyl)amino]phenyl}  
30    benzenesulfonamide,  
         N-{4-(1-piperazinyl)-2-[(phenylsulfonyl)amino]phenyl}-1-naphthalenesulfonamide,

5-(dimethylamino)-N-{4-(1-piperazinyl)-2-[(phenylsulfonyl)amino]phenyl}-1-naphthalenesulfonamide,  
N-[2-[(phenylsulfonyl)amino]-4-(1-piperazinyl)phenyl]-8-quinolinesulfonamide,  
2,4,6-trimethyl-N-[2-[(phenylsulfonyl)amino]-4-(1-piperazinyl)phenyl]  
5 benzenesulfonamide,  
4-methyl-N-[2-[(phenylsulfonyl)amino]-4-(1-piperazinyl)phenyl] benzenesulfonamide,  
N-[2-({[(E)-2-phenylethenyl}sulfonyl)amino]-5-(1-piperazinyl)phenyl]  
benzenesulfonamide,  
2,5-dimethoxy-N-[2-[(phenylsulfonyl)amino]-4-(1-piperazinyl)phenyl]  
10 benzenesulfonamide,  
2-methyl-N-[2-[(phenylsulfonyl)amino]-4-(1-piperazinyl)phenyl] benzenesulfonamide,  
2,4-difluoro-N-[2-[(phenylsulfonyl)amino]-4-(1-piperazinyl)phenyl]  
benzenesulfonamide,  
4-butoxy-N-[2-[(phenylsulfonyl)amino]-4-(1-piperazinyl)phenyl]benzenesulfonamide,  
15 3,5-dimethyl-N-[2-[(phenylsulfonyl)amino]-4-(1-piperazinyl)phenyl]-4-isoxazolesulfonamide,  
5-fluoro-2-methyl-N-[2-[(phenylsulfonyl)amino]-4-(1-piperazinyl)phenyl]  
benzenesulfonamide,  
4-(methylsulfonyl)-N-[2-[(phenylsulfonyl)amino]-4-(1-piperazinyl)phenyl]  
20 benzenesulfonamide,  
2-(methylsulfonyl)-N-[2-[(phenylsulfonyl)amino]-4-(1-piperazinyl)phenyl]  
benzenesulfonamide,  
2-methoxy-4-methyl-N-[2-[(phenylsulfonyl)amino]-4-(1-piperazinyl)phenyl]  
benzenesulfonamide,  
25 4-methoxy-2-methyl-N-[2-[(phenylsulfonyl)amino]-4-(1-piperazinyl)phenyl]  
benzenesulfonamide,  
N-[2-amino-4-(1-piperazinyl)phenyl]-3-fluorobenzenesulfonamide,  
N-[2-(ethylamino)-4-(1-piperazinyl)phenyl]-3-fluorobenzenesulfonamide,  
N-{4-(1,4-diazepan-1-yl)-2-[(phenylsulfonyl)amino]phenyl}benzenesulfonamide  
30 hydrochloride

N-(4-(1,4-diazepan-1-yl)-2-{[(3-fluorophenyl)sulfonyl]amino}phenyl)-3-fluorobenzenesulfonamide hydrochloride

N-{5-(1,4-diazepan-1-yl)-2-[(phenylsulfonyl)amino]phenyl}-N-ethylbenzenesulfonamide hydrochloride

5 N-{5-(1,4-diazepan-1-yl)-2-[(methylsulfonyl)amino]phenyl}benzenesulfonamide hydrochloride

N-{5-(1,4-diazepan-1-yl)-2-[(ethylsulfonyl)amino]phenyl}benzenesulfonamide hydrochloride

N-{4-(1,4-diazepan-1-yl)-2-[(phenylsulfonyl)amino]phenyl}[1,1'-biphenyl]-4-sulfonamide hydrochloride

10 N-{4-(1,4-diazepan-1-yl)-2-[(phenylsulfonyl)amino]phenyl}-2,1,3-benzoxadiazole-4-sulfonamide hydrochloride

N-{4-(1,4-diazepan-1-yl)-2-[(phenylsulfonyl)amino]phenyl}-2-naphthalenesulfonamide hydrochloride

15 N-{4-(1,4-diazepan-1-yl)-2-[(methylsulfonyl)amino]phenyl}benzenesulfonamide hydrochloride

N-{4-(1,4-diazepan-1-yl)-2-[methyl(methylsulfonyl)amino]phenyl}benzenesulfonamide hydrochloride

N-{4-(1,4-diazepan-1-yl)-2-[(methylsulfonyl)amino]phenyl}-N-methylbenzenesulfonamide hydrochloride

20 N-{4-(1,4-diazepan-1-yl)-2-[(methylsulfonyl)amino]phenyl}-1-naphthalenesulfonamide hydrochloride

N-{4-(1,4-diazepan-1-yl)-2-[(methylsulfonyl)amino]phenyl}-2-naphthalenesulfonamide hydrochloride

25 N-{4-(1,4-diazepan-1-yl)-2-[(methylsulfonyl)amino]phenyl}-4-fluorobenzenesulfonamide hydrochloride

N-{4-(1,4-diazepan-1-yl)-2-[(methylsulfonyl)amino]phenyl}-4-nitrobenzenesulfonamide hydrochloride

30

N-{4-(1,4-diazepan-1-yl)-2-[(methylsulfonyl)amino]phenyl}-3-(trifluoromethyl)benzenesulfonamide hydrochloride

N-{4-(1,4-diazepan-1-yl)-2-[(methylsulfonyl)amino]phenyl}-2-methylbenzenesulfonamide hydrochloride

5 N-{4-(1,4-diazepan-1-yl)-2-[(methylsulfonyl)amino]phenyl}-4-(trifluoromethoxy)benzenesulfonamide hydrochloride

N-{4-(1,4-diazepan-1-yl)-2-[(methylsulfonyl)amino]phenyl}-3,5-dimethyl-4-isoxazolesulfonamide hydrochloride

N-{4-(1,4-diazepan-1-yl)-2-[(methylsulfonyl)amino]phenyl}-3-methoxybenzenesulfonamide hydrochloride

10 N-{4-(1,4-diazepan-1-yl)-2-[(methylsulfonyl)amino]phenyl}-4-methylbenzenesulfonamide hydrochloride

N-{4-(1,4-diazepan-1-yl)-2-[(methylsulfonyl)amino]phenyl}-2-[ethyl(methylsulfonyl)amino]phenyl}-4-methylbenzenesulfonamide hydrochloride

15 N-{4-(1,4-diazepan-1-yl)-2-[ethyl(methylsulfonyl)amino]phenyl}-3,4-dimethoxybenzenesulfonamide hydrochloride

N-{4-(1,4-diazepan-1-yl)-2-[ethyl(methylsulfonyl)amino]phenyl}-7-quinolinesulfonamide hydrochloride

N-{4-(1,4-diazepan-1-yl)-2-[methyl(methylsulfonyl)amino]phenyl}-4-methylbenzenesulfonamide hydrochloride

20 N-{4-(1,4-diazepan-1-yl)-2-[methyl(methylsulfonyl)amino]phenyl}-1-naphthalenesulfonamide hydrochloride

N-{4-(1,4-diazepan-1-yl)-2-[methyl(methylsulfonyl)amino]phenyl}-5-(2-pyridinyl)-2-thiophenesulfonamide hydrochloride

25 N-{4-(1,4-diazepan-1-yl)-2-[(phenylsulfonyl)amino]phenyl}-1-naphthalenesulfonamide hydrochloride

N-{4-(1,4-diazepan-1-yl)-2-[(phenylsulfonyl)amino]phenyl}-5-(dimethylamino)-1-naphthalenesulfonamide hydrochloride

N-{4-(1,4-diazepan-1-yl)-2-[(phenylsulfonyl)amino]phenyl}-8-quinolinesulfonamide hydrochloride

30

N-{4-(1,4-diazepan-1-yl)-2-[(phenylsulfonyl)amino]phenyl}-2,4,6-trimethylbenzenesulfonamide hydrochloride

N-{4-(1,4-diazepan-1-yl)-2-[(phenylsulfonyl)amino]phenyl}-4-methylbenzenesulfonamide hydrochloride

5 N-[5-(1,4-diazepan-1-yl)-2-({[(E)-2-phenylethenyl]sulfonyl}amino)phenyl]benzenesulfonamide hydrochloride

N-{4-(1,4-diazepan-1-yl)-2-[(phenylsulfonyl)amino]phenyl}-2,5-dimethoxybenzenesulfonamide hydrochloride

N-{4-(1,4-diazepan-1-yl)-2-[(phenylsulfonyl)amino]phenyl}-2-methylbenzenesulfonamide hydrochloride

10 4-butoxy-N-{4-(1,4-diazepan-1-yl)-2-[(phenylsulfonyl)amino]phenyl}benzenesulfonamide hydrochloride

N-{4-(1,4-diazepan-1-yl)-2-[(phenylsulfonyl)amino]phenyl}-3,5-dimethyl-4-isoxazolesulfonamide hydrochloride

15 N-{4-(1,4-diazepan-1-yl)-2-[(phenylsulfonyl)amino]phenyl}-5-fluoro-2-methylbenzenesulfonamide hydrochloride

N-{4-(1,4-diazepan-1-yl)-2-[(phenylsulfonyl)amino]phenyl}-4-(methylsulfonyl)benzenesulfonamide hydrochloride

N-{4-(1,4-diazepan-1-yl)-2-[(methylsulfonyl)amino]phenyl}-N-methylbenzenesulfonamide hydrochloride

20 N-{5-(1,4-diazepan-1-yl)-2-[methyl(phenylsulfonyl)amino]phenyl}-4-methylbenzenesulfonamide hydrochloride

3-amino-4-(1,4-diazepan-1-yl)-N-(4-methoxyphenyl)benzenesulfonamide hydrochloride

3-amino-4-(1,4-diazepan-1-yl)-N-(3-methoxyphenyl)benzenesulfonamide hydrochloride

25 3-amino-4-(1,4-diazepan-1-yl)-N-(2-methoxyphenyl)benzenesulfonamide hydrochloride

3-amino-4-(1,4-diazepan-1-yl)-N-(3-fluorophenyl)benzenesulfonamide hydrochloride

3-amino-4-(1,4-diazepan-1-yl)-N-methyl-N-phenylbenzenesulfonamide hydrochloride

3-amino-4-(1,4-diazepan-1-yl)-N-(4-isopropylphenyl)benzenesulfonamide hydrochloride

3-amino-4-(1,4-diazepan-1-yl)-N-(4-methylphenyl)benzenesulfonamide hydrochloride

30 3-amino-4-(1,4-diazepan-1-yl)-N-(2,5-dimethylphenyl)benzenesulfonamide hydrochloride

3-amino-N-(3-chlorophenyl)-4-(1,4-diazepan-1-yl)benzenesulfonamide hydrochloride

3-amino-N-(2-chlorophenyl)-4-(1,4-diazepan-1-yl)benzenesulfonamide hydrochloride

3-amino-N-(2,4-dichlorophenyl)-4-(1,4-diazepan-1-yl)benzenesulfonamide hydrochloride

3-amino-N-(2-methyl-5-chloro-phenyl)-4-(1,4-diazepan-1-yl)benzenesulfonamide hydrochloride

5 3-amino-N-(2-methyl-3-chloro-phenyl)-4-(1,4-diazepan-1-yl)benzenesulfonamide hydrochloride

3-amino-N-(4-trifluoro-phenyl)-4-(1,4-diazepan-1-yl)benzenesulfonamide hydrochloride

3-amino-N-(4-fluorophenyl)-4-(1,4-diazepan-1-yl)benzenesulfonamide hydrochloride

3-amino-N-(2-fluorophenyl)-4-(1,4-diazepan-1-yl)benzenesulfonamide hydrochloride

10 3-amino-4-(4-methyl-1,4-diazepan-1-yl)-N-phenylbenzenesulfonamide hydrochloride

4-(1,4-diazepan-1-yl)-3-nitro-N-phenylbenzenesulfonamide hydrochloride

3-amino-4-(1,4-diazepan-1-yl)-N-phenylbenzenesulfonamide hydrochloride

2-(1,4-diazepan-1-yl)-5-(4-morpholinylsulfonyl)phenylamine hydrochloride

4-(1,4-diazepan-1-yl)-N-phenyl-3-[(phenylsulfonyl)amino]benzenesulfonamide

15 hydrochloride

4-(1,4-diazepan-1-yl)-N-phenyl-3-[(methylsulfonyl)amino]benzenesulfonamide hydrochloride

3-amino-N-(3-chlorophenyl)-4-(4-methyl-1-piperazinyl)benzenesulfonamide hydrochloride

3-amino-N-(2-methoxyphenyl)-4-(4-methyl-1-piperazinyl)benzenesulfonamide

20 hydrochloride

3-amino-N-(2-methoxyphenyl)-4-(1-piperazinyl)benzenesulfonamide hydrochloride

3-amino-N-(2-methoxyphenyl)-4-(3-methyl-1-piperazinyl)benzenesulfonamide hydrochloride

3-Amino-4-(hexahydro-pyrrolo[1,2-a]pyrazin-2-yl)-N-(2-methoxyphenyl)-

25 benzenesulfonamide hydrochloride

3-Amino-N-phenyl-4-piperazin-1-yl-benzenesulfonamide hydrochloride

3-Amino-4-(3-methyl-piperazin-1-yl)-N-phenyl-benzenesulfonamide hydrochloride

3-Amino-4-(4-ethyl-piperazin-1-yl)-N-phenyl-benzenesulfonamide hydrochloride

3-Amino-4-(hexahydro-pyrrolo[1,2-a]pyrazin-2-yl)-N-phenyl-benzenesulfonamide hydrochloride

3-Amino-4-(5-methyl-2,5-diaza-bicyclo[2.2.1]hept-2-yl)-N-phenyl-benzenesulfonamide hydrochloride

5 3-Amino-4-(trans -2,5-dimethyl-piperazin-1yl)-N-(2methoxy-phenyl)benzenesulfonamide hydrochloride

2-(3-Amino-4-[1,4]diazepan-1-yl-benzenesulfonyl)-benzamide diacetic acid

4-[4-(3-Fluoro-2-methoxy-phenylsulfamoyl)-2-amino-phenyl]-[1,4]diazepane

ditrifluoroacetic acid

10 2-[1,4]Diazepan-1-yl-5-(3,4-dihydro-1H-isoquinoline-2-sulfonyl)-aniline dihydrochloride

4-[4-(3,4-Dihydro-2H-quinoline-1-sulfonyl)-2-amino-phenyl]-[1,4]diazepane

ditrifluoroacetic acid

3-Amino-2-chloro-N-naphthalen-1-yl-4-piperazin-1-yl-benzenesulfonamide, hydrochloride

15 9. A process for the preparation of a compound according to any one of claims 1 to 8 comprising:

(a) introduction of a cyclic diamine into halogen and nitro substituted benzene under mild and basic conditions;

(b) reduction of the nitro to the corresponding amine;

20 (c) symmetric or asymmetric sulfonylation of the amine by a sulfonylchloride;

(d) introduction of groups R<sup>3</sup> and R<sup>4</sup> by alkylation procedure in basic conditions.

10. A pharmaceutical formulation containing a compound of any one of claims 1 to 8 as an active ingredient, in combination with a pharmaceutically acceptable diluent or carrier.

25

11. A method for the treatment or prophylaxis of obesity, type II diabetes, or disorders of the central nervous system, comprising administering to a mammal in need of such treatment an effective amount of a compound of any one of claims 1 to 8.

30 12. A method for modulating 5-HT<sub>6</sub> receptor activity, comprising administering to a mammal in need thereof an effective amount of a compound of any one of claims 1 to 8.

13. A compound according to any one of claims 1 to 8 for use in therapy.

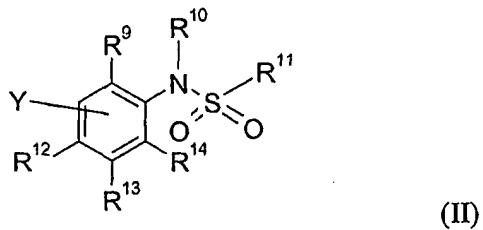
14. A compound according to any one of claims 1 to 8 for use in the treatment or prophylaxis  
5 of obesity, type II diabetes, and/or disorders of the central nervous system.

15. Use of a compound according to any one of claims 1 to 8 for the manufacture of a  
medicament for use in the treatment or prophylaxis of obesity, type II diabetes, and/or  
disorders of the central nervous system.

10

16. A pharmaceutical formulation for use in the treatment or prophylaxis of obesity, type II  
diabetes, and/or disorders of the central nervous system wherein the active ingredient is a  
compound according to any one of claims 1 to 11.

15 17. A compound of the formula (II)



or a pharmaceutically acceptable salt thereof, wherein

20

$\text{R}^9$ ,  $\text{R}^{12}$  and  $\text{R}^{14}$  are H; or

two of  $\text{R}^9$ ,  $\text{R}^{12}$  and  $\text{R}^{14}$  are H; and the remaining of  $\text{R}^9$ ,  $\text{R}^{12}$  and  $\text{R}^{14}$  is

(a)  $-\text{NH}_2$ ,

(b)  $-\text{NHR}^6$ ,

25 (c)  $-\text{NR}^6\text{R}^7$ ,

(d)  $-\text{N}(\text{CO})\text{R}^6$ ,

(e)  $-\text{N}(\text{CS})\text{R}^6$ , or

(f)  $\text{--NO}_2$ ;

$\text{R}^{10}$  is a group  $\text{R}^3$  as defined for the formula (I) in claim 1;

5      $\text{R}^{11}$  is a group  $\text{R}^1$  as defined for the formula (I) in claim 1;

$\text{R}^{13}$  is

(a) homopiperazine,

(b) methylhomopiperazine, or

10   (c) a group  $\text{R}^5$  as defined for the formula (I) in claim 1, wherein  $\text{R}^8$  is as defined for the formula (I) in claim 1; and

$\text{Y}$  is as defined for the formula (I) in claim 1, and

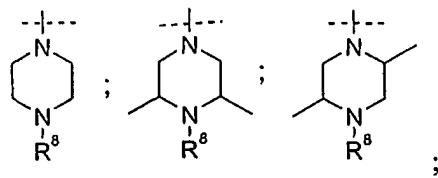
15   each of  $\text{R}^6$  and  $\text{R}^7$ , independently, is as defined for the formula (I) in claim 1.

18. A compound according to claim 17 wherein  $\text{R}^{13}$  is

(a) homopiperazine,

(b) methylhomopiperazine, or

20   (c) a group  $\text{R}^5$  selected from



and

$\text{R}^8$  is

25   (a) H, or

(b)  $\text{C}_{1-6}$  alkyl, in particular methyl;

with the proviso that only one of R<sup>9</sup>, R<sup>12</sup> and R<sup>14</sup> is -NH<sub>2</sub>, -NHR<sup>6</sup>, -NR<sup>6</sup>R<sup>7</sup>, -N(CO)R<sup>6</sup>, -N(CS)R<sup>6</sup>, -NO<sub>2</sub>; the other ones are H.

19. A compound according to claim 17 which is the compound

5        4-chloro-N-[5-(4-methyl-1,4-diazepan-1-yl)-2-nitrophenyl]benzenesulfonamide,  
N-[2-amino-5-(1,4-diazepan-1-yl)phenyl]benzenesulfonamide,  
N-[2-amino-5-(4-methyl-1,4-diazepan-1-yl)phenyl]benzenesulfonamide,  
N-[4-nitro-5-(piperazinyl)phenyl]benzenesulfonamide, or  
N-[4-amino-5-(piperazinyl)phenyl]benzenesulfonamide.

10

20. A process for the preparation of a compound according to any one of claims 17 to 19 comprising:

(a) introduction of a cyclic diamine into halogen and nitro substituted benzene under mild and basic conditions;  
15        (b) reduction of the nitro to the corresponding amine;  
(c) selective introduction of a sulfonylamide group by a sulphonylchloride reacting with the amine;  
(d) introduction of a sulfonylanimo group by aromatic nucleophilic substitution.

20        21. A pharmaceutical formulation containing a compound according to any one of claims 17 to 19 as an active ingredient, in combination with a pharmaceutically acceptable diluent or carrier.

25        22. A method for the treatment or prophylaxis of obesity, type II diabetes, or disorders of the central nervous system, comprising administering to a mammal, in need of such treatment an effective amount of a compound according to any one of claims 17 to 19.

23. A method for modulating 5-HT<sub>6</sub> receptor activity, comprising administering to a mammal in need thereof an effective amount of a compound according to any one of claims 17 to 19.

30

24. A compound according to any one of claims 17 to 19 for use in therapy.

25. A compound according to any one of claims 17 to 19 for use in the treatment or prophylaxis of obesity, type II diabetes, and/or disorders of the central nervous system.

5    26. Use of a compound according to any one of claims 17 to 19 for the manufacture of a medicament for use in the treatment or prophylaxis of obesity, type II diabetes, and/or disorders of the central nervous system.

10    27. A pharmaceutical formulation for use in the treatment or prophylaxis of obesity, type II diabetes, and/or disorders of the central nervous system wherein the active ingredient is a compound according to any one of claims 17 to 19.

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 02/00906

**A. CLASSIFICATION OF SUBJECT MATTER**  
C07D 295/04, C07D 241/04, C07D 211/46, C07D 233/56, C07D 243/08, C07D 215/36, C07D 453/02, C07D 487/04,  
C07D 487/08, A61K 31/495, A61K 31/551, A61K 31/4164, A61K 31/445, A61K 31/439, A61K 31/496, A61P 3/04,  
IPC7: A61P 3/10, A61P 25/00, A61P 5/48  
According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07D, A61K, A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CHEM.ABS.DATA, WPI DATA, EPO-INTERNAL

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DE 2239846 A (FARBWERKE HOECHST AG), 14 February 1974 (14.02.74)  --	1,3,5-7
X	DE 2334562 A (FARBWERKE HOECHST AG), 30 January 1975 (30.01.75)  --	1,3,5-7
X	DE 2459394 A (HOECHST AG), 24 June 1976 (24.06.76)  --	1-3,5-7
X	WO 0116094 A1 (AVENTIS PHARMA DEUTSCHLAND GMBH), 8 March 2001 (08.03.01)  --	1-3,5-7

 Further documents are listed in the continuation of Box C. See patent family annex.

- \* Special categories of cited documents:
- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier application or patent but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed
- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- "&" document member of the same patent family

Date of the actual completion of the international search  <u>12 August 2002</u>	Date of mailing of the international search report  <u>23 -08- 2002</u>
Name and mailing address of the ISA Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. + 46 8 666 02 86	Authorized officer  VIVECA NORÉN/BS Telephone No. + 46 8 782 25 00

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 02/00906

## C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 0116096 A2 (AVENTIS PHARMA DEUTSCHLAND GMBH), 8.March 2001 (08.03.01) --	1-3,5-7
X	FR 2033597 A (UGINE KUHLMANN), 4 December 1970 (04.12.70) --	1
X	Arzneimittel-Forschung, Volume 19 (1969), No.10, Par G. Régnier et al: "Étude chimique et pharmacologique de nouveaux dérivés de la nor-Adrenaline", pages 1698-1702 --	17-18
X	WO 9942465 A2 (SMITHKLINE BEECHAM PLC), 26 August 1999 (26.08.99) --	1-27
X	WO 9827081 A1 (SMITHKLINE BEECHAM PLC), 25 June 1998 (25.06.98) --	1-27
X	EP 0815861 A1 (F. HOFFMANN-LA ROCHE AG), 7 January 1998 (07.01.98) --	1-27
X	WO 0012073 A1 (SMITHKLINE BEECHAM P.L.C.), 9 March 2000 (09.03.00) --	1-27
X	WO 0012623 A2 (SMITHKLINE BEECHAM P.L.C.), 9 March 2000 (09.03.00) --	1-27
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## INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 02/00906

## C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X	WO 9806697 A1 (SCHERING CORPORATION), 19 February 1998 (19.02.98) --	1-27
X	WO 9938845 A1 (TULARIK INC.), 5 August 1999 (05.08.99) --	1-27
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International application No.  
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## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.: **11-12 and 22-23**  
because they relate to subject matter not required to be searched by this Authority, namely:  
**see next sheet**
2.  Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3.  Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1.  As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3.  As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4.  No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

### Remark on Protest

The additional search fees were accompanied by the applicant's protest.  
 No protest accompanied the payment of additional search fees.

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Claims 11-12 and 22-23 relate to methods of treatment of the human or animal body by surgery or by therapy/ diagnostic methods practised on the human or animal body/Rule 39.1.(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.

**INTERNATIONAL SEARCH REPORT**

Information on patent family members

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International application No.

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